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FINAL REPORT
of a study on
Relationship of airborne manganese exposure to neurobehavioral and health status of adults

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Objective

The objective of this study was to investigate whether there is a relationship between airborne manganese (Mn) exposure and adverse neurobehavioral and health effects among adult residents of a manganese-exposed community. Specifically, the current study aimed to answer the following questions:

- Is there is a relationship of Mn levels in blood (Mn/B) (internal) or Mn levels in air (Mn/air) (external) and neurobehavioral function in adults?

- Does the neurobehavioral function of a group of Mn-exposed adults (Marietta, Oh) differ significantly from that of a demographically similar group of minimally exposed adults (Mount Vernon, OH)?

Summary/Accomplishments

Data collection was conducted in August, 2009. Following a period of data preparation (scoring, double-scoring, entry, double-entry, and clean-up), the data analyses performed to answer the above questions have resulted in:

- a feedback meeting with the Ohio Department of Health (ODH)
- a feedback meeting with the community of Marietta, OH (the exposed town)
- individualized feedback letters to each study participant
- numerous presentations to the scientific community (described below)
- several peer-reviewed publications (described below)

Conclusions

Overall, results of this epidemiologic study using random sampling did not support findings of adverse health effects from levels of Mn in air and levels of Mn in blood in the town of Marietta. This is supported by the lack of differences in neurobehavioral test scores between Marietta and Mount Vernon participants. Although proximity to the point source was related to worse scores on some tests of visual memory and processing speed, overall the test results for both towns did not differ and were within the average range of the general population.

Introduction

Exposure Background

In 2000, the Agency for Toxic Substances and Disease Registry (ATSDR) initiated a public health assessment for the Marietta Air Emissions Site (Ohio). Air monitoring in the region identified airborne Mn as the main environmental exposure of concern.
Eramet Marietta, Inc (EMI) is the major historic producer of Mn ferroalloys in the region and is one of the largest Mn-manufacturing facilities in the world. Historically, EMI ranks first in total air

releases of Mn and Mn compounds among all U.S. facilities reporting to the USEPA Toxic Release Inventory (TRI) (U.S. EPA, 2010).

The ATSDR has determined that long-term ambient Mn concentrations in the area exceed the USEPA reference concentration (RfC = 0.05 µg/m3) and minimal risk level (MRL = 0.04 µg/m3) (ATSDR, 2009).

Human Exposure to Manganese

In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners and chemical workers who are over-exposed to Mn, a major component in iron/steel welding fumes, are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health and cognitive ability and a movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, and dystonia, bradykinesia, tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. This is the 1st comprehensive environmental study of Mn-exposed adults in the U.S.

Design

This study used a **cross-sectional control/exposed** design of recruiting up to 100 Mn-exposed and 100 control (low-exposed) adults between the ages of 30-75 years. The study includes data on air monitoring and modeling, biomarkers, health, and neuropsychological and neurological assessments of participants from both groups.

Recruitment procedure

Participants were randomly selected using property tax records, from the Mn-exposed town of Marietta, and the low-exposed comparison town of Mount Vernon (OH). Recruitment letters describing the study were mailed to 1,732 households from Marietta and 2,207 household from Mount Vernon. A response card, stamped and addressed to the study office, was included for the potential participant to complete and return if interested in participating. Of the 3,939 letters sent, 308 were undeliverable and returned (160 from Marietta, 148 from Mount. Vernon). Response cards indicating interest were received from 207 potential participants (106 from Marietta and 101 from Mount Vernon). Researchers also attempted to contact by telephone all potential participants who were sent letters and did not return the response card and asked if they were interested in study participation. All 509 participants who indicated interest in the study (264 from Marietta, 245 from Mount Vernon), either through email, response cards, or when called on the telephone, were given a screening questionnaire. In total, 270 respondents to the random mailings were excluded based on the study's exclusion criteria, or were unable to participate. One-hundred participants from each town were scheduled for testing, along with 5 alternates for each town. One-hundred participants from Marietta and 91 from Mount Vernon were tested. One participant tested in Mount Vernon did not meet the inclusion criteria, and was excluded from analyses. Participants were given $50 gift certificates for their participation. Following completion of the data analysis phase, feedback letters were sent to all participants and a community meeting was held to present group results. Group results were also presented at a separate meeting with representatives of the Ohio Department of Health.

Testing procedure

Dr. Rosemarie Bowler was successful in obtaining the collaboration and participation of Dr. Harry Roels (neurotoxicologists and blood sample processing), Dr. Yangho Kim (neurology and UPDRS) and Dr. Nadia Abdelouahab (CATSYS). Two neuropsychologists and 6 trained graduate students administered the neuropsychological tests. The battery included tests shown

to be sensitive to Mn exposure, including measures of Cognitive flexibility (ROCF, Trailmaking B), Information Processing (Stroop), Working Memory and Attention (ACT), Memory (NAB Memory Module), Visuomotor tracking speed (Digit Symbol Coding), Verbal skills (Similarities, Animal Naming), Motor efficiency and strength (Fingertapping, Grooved Pegboard, Dynamometer), and tremor (CATSYS, UPDRS). In addition, work histories and health questionnaires were administered.

Exposure assessment

Blood samples from participants were analyzed at the CDC National Laboratory for levels of manganese, cadmium, lead, and mercury. Serum samples were analyzed at U.S. EPA NHEERL Core Lab for levels of ferritin – and indicator of iron store in the body

Air dispersion modeling was conducted using 2001 emissions information, receptors, and meteorological data to calculate estimated Mn concentrations near various residences in Marietta. This was used to create a hazard quotient (a ratio of modeled concentrations to the Mn reference concentration) and a cumulated exposure index (CEI – the product of modeled concentration and duration of residence in Marietta), two ways of estimating a participant's exposure to airborne Mn.

Results

As is shown in Figures 1 and 2, the large effort of contacting a sufficient number of residents in both towns resulted in 100 residents being tested in Marietta and 90 residents in Mount Vernon (due to no-shows on the days of testing in Ohio). The participants from the two towns were very similar demographically (Bowler et al., 2011). The enclosed Table 1 shows the demographics and biomarkers for both Marietta and Mount Vernon and Tables 2 & 3 list the means, medians, ranges, and t-test analyses comparing the towns on demographic and biomarker variables stratified by gender.

The extensive and comprehensive health questionnaire was analyzed and Table 4 displays the symptom categories by town. It can be noted that Marietta residents complained more about motor, visual, and anxiety symptoms. The illnesses listed in the health questionnaire were categorized using ICD-9 codes and, as can be seen in Table 5, there were no differences between the towns on the prevalence of doctor-diagnosed illnesses.

As shown in Tables 1-3, levels of Mn in blood, serum ferritin and blood levels of lead, mercury, and cadmium were largely in the normal range and did not differ by town (Bowler et al., 2011).

No significant differences between the towns were found for any neurobehavioral tests (Table 6), which included tests of motor speed, motor strength and tremor, attention and immediate memory, switching categories and divided attention, visual delayed memory, and verbal delayed memory. Scores in both towns were within the average range.

Although there was not a consistent relationship between levels of Mn in blood and neurobehavioral performance (in either town), higher exposure to Mn in the air (hazard quotient and CEI) was related to worse performance on some tests, particularly tests of executive functions.

No significant differences were found between the towns on mood disturbance, except for levels of phobic anxiety being higher in Marietta (Figure 3) (Bowler et al., 2011). Overall, there was not a consistent relationship between levels of Mn in blood and mood, although higher hazard quotients were related to higher phobic anxiety and higher CEI was related to higher obsessive-compulsive, anxiety, phobic anxiety, and paranoid ideation symptoms. Using a composite score to indicate generalized anxiety, higher CEI was related to higher generalized anxiety (Bowler et al., 2011). This composite anxiety score was also related to neurological outcomes on the UPDRS.

Although there were no significant differences between participants of the two towns in the prevalence of illnesses categorized into ICD-9 categories (Table 5), some individual symptoms were reported significantly more frequently in Marietta: changes in sense of smell or taste, headaches overall, headaches in the presence of gas, headaches in the presence of paint, tightness of facial muscles, feeling anxious, feeling irritable, changes in personality, excessive perspiration, fever or chills, and nausea.

Mn in blood was related to more frequent endocrine and psychological illness in Marietta. The hazard quotient was related to excessive perspiration but showed no consistent relationships with illnesses or other symptoms. The CEI did not show consistent relationships with illnesses or symptoms.

On a neurological examination, the UPDRS, Marietta participants had slower movement and motor speed than Mount Vernon participants. No relationship between exposure variables were found with UPDRS scores (Kim et al., 2011).

As shown above in Table 7, there was no difference in dietary Mn intake between the two towns, and Mn in diet was not related to Mn in blood or to any outcome variables.

Additional funding through a contract with U.S. EPA has been obtained to collect data from an additional town that has had historically very high levels of air Mn concentrations. We will use the data obtained from this grant (Marietta and Mount Vernon, OH) to compare data collected from this third town.

Key Research Accomplishments

1. A symposium was presented at the 26th International Neurotoxicology Conference, June 8th, 2010 in Portland, OR including the following presentations prepared with data from the study:

   Methodological aspects of an epidemiologic study of adults living near a Mn point source, Bowler, R. M., Kim, Y., Ngo, L., Roels, H. A. (Appendix A).

   Relationships between mood and neuropsychological performance in adults with environmental exposure to manganese, Harris, M., Bowler, R. (Appendix B)

2. Dr. Bowler gave an invited presentation to the Marietta community, June 24th, 2010 in Marietta, OH, entitled:

   Health Study of Manganese Exposure of Adults in Marietta & Mount Vernon, Ohio: Preliminary Results (see Appendix C)**.**

3. Dr. Bowler gave an invited presentation to the Ohio Department of Health, June 24th, 2010 in Columbus, OH, entitled:

   Relationship of residential airborne manganese exposure to neuropsychological, neurological and health status of adults (Appendix D).

4. Dr. Bowler and her colleagues/collaborators presented a symposium at the International Neuropsychological Society meeting in Boston, MA on February 5th, 2011, on the neuropsychological test results in relation to Mn exposure including the following presentations prepared with data from the study:

Manganese Exposure in Adults: An Epidemiologic Study of Symptoms, Mood Effects, Motor and Neurological Function, Bowler, R. (Appendix E)

Manganese Exposure and Components of Executive Function in Environmentally-Exposed Adults, Harris, M., Bowler, R. (Appendix F).

5. Dr. Bowler gave an invited presentation on the overall results of the Marietta study at the 13th Meeting of the International Neurotoxicology Association, June 5th – 10, 2011, Xian, China. Highlights were the neurotoxicological aspects of the study:

Relationship of airborne manganese exposure to biomarkers of blood and serum controlled for ferritin with neurological and neuropsychological test results in adults, Bowler, R. (Appendix G)

6. Dr. Bowler supervised a doctoral dissertation reporting data from the Marietta/Mount Vernon study:

Harris, M. (2011) Manganese Neurotoxicity: Relationships Between Exposure, Executive Function, and Mood Among Environmentally-Exposed Adults. ***Dissertation Abstracts International*** (Appendix H)

7. A peer-reviewed manuscript is currently in press:

Bowler, R. ***et al*****. (2011, in press) Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure.** ***International Journal of Hygiene and Environmental Health.*** (Appendix I)

8. A peer-reviewed manuscript has been published:

Kim, Y. ***et al.*** **(2011) Motor function in adults of an Ohio community with environmental manganese exposure.** ***Neurotoxicology*****, 32** ***(5)*****: 606-14** (Appendix J)

9. Dr. Bowler and the study team submitted a proposal and subsequently received funding to replicate the study in residents near a Mn-processing plant in East Liverpool, OH. Three ambient air monitors have collected measurements in this community for the last 10 years. This study is currently taking place. The exact same test battery was administered to Mn-exposed residents of East Liverpool and the same laboratories conducted the analyses of biomarkers for East Liverpool. The Mn exposure in air is reported to be significantly higher in East Liverpool than in Marietta; in fact, East Liverpool has the highest measured Mn air levels in the U.S., but the Mn particle sizes are somewhat larger than those found in Marietta. This difference will be taken into account in the current work when constructing a Cumulative Exposure Index. The results will be added to those of the current study, and three-way comparisons on participants from the three towns will determine the effects of a gradient of exposure and if there are significant relationships between Mn in air and health effects.

Tables:

Table 1. Demographics and Biomarkers - Whole sample

			Marietta				Range		Mt. Vernon				Range		t-tests	
			n	Mean (%)	SD	Median	Min	Max	n	Mean (%)	SD	Median	Min	Max	t-statistic (χ^2)	sig
Demographics																
	Age		100	54.42	9.86	55.50			90	55.53	10.96	55.50	32	75	0.74	0.46
	Years of Education		100	14.55	2.69	14.00			90	15.18	3.04	14.00	12	22	1.51	0.13
	Years in Town		100	36.07	15.75	37.00			90	33.59	17.25	31.00	10	74	-1.04	0.30
	Gender														(.006)	(.939)
		Male	45	45%					40	44%						
		Female	55	55%					50	56%						
	Current Smokers		20	20%					18	20%						
	Ethnicity														(2.08)	(0.56)
		African-American	2	2%					2	2.2%						
		Caucasian	94	94%					87	96.7%						
		Asian-American	2	2%												
		Native American	2	2%					1	1.1%						
	Marital Status														(1.656)	(0.799)
		Single	6	6%					6	7%						
		Married	81	81%					68	76%						
		Divorced	11	11%					12	13%						
		Widowed	1	1%					3	3%						
		Co-habitating	1	1%					1	1%						
	Household Income ($ / yr)														(6.702)	(0.753)
		0 - 29,999	26	28.30%					14	16.60%						
		30,000 - 59,999	28	30.40%					32	38.10%						
		60,000 - 89,999	19	20.60%					19	22.60%						
		90,000 and above	19	20.60%					19	22.60%						
	Work History														(6.677)	(0.083)
		Employed	63						61	67.78%						
		Unemployed/Retired	31						28	31.11%						
		Student	0	0					1	1.11%						
		Disabled	6						0	0						
Biomarkers																
	Blood Mn(µg/L)		100	9.7	3.2	9.2	4.91	24.6	90	9.5	3.2	8.8	3.75	18.90		
	Natural log of Mn		100	2.22	0.30	2.21	1.59	3.20	90	2.20	0.33	2.17	1.32	2.94	-0.55	0.59
	Blood Cd (µg/L)		100	0.53	0.53	0.31	0.14	2.87	90	0.47	0.54	0.30	0.00	4.06	-0.83	0.46
	Blood Hg (µg/L)		100	1.38	1.89	0.77	0.23	14.6	90	0.96	1.26	0.66	0.23	9.75	-1.80	0.08
	Blood Pb (µg/dL)		100	1.56	0.95	1.30	0.32	5.39	90	1.41	0.95	1.14	0.31	5.96	-1.09	0.28
	Serum ferritin (ng/mL)		100	132.18	153.25	76.25	12.20	#####	90	130.64	111.23	89.95	7.69	####	-0.08	0.94
	Natural log of ferritin		100	4.42	0.94	4.33	2.50	6.75	90	4.51	0.91	4.50	2.04	6.32	*0.69*	*0.49*
Distance from point source			100	4.75	1.64	4.50	0.99	11.00								
Air concentration of Mn			100	0.18	0.13	0.16	0.04	0.96								
Hazard Quotient			100	3.69	2.62	3.14	0.77	19.17								
CEI			100	6.67	5.90	5.53	0.89	41.22								

* *Italics* = equal variances not assumed

Table 2. Demographics and biomarkers gender comparison between towns (Males)

	MALES											
	Marietta					**Mt Vernon**					**t-tests**	
	n	Mean (%)	SD	Median	Range	n	Mean (%)	SD	Median	Range	t-statistic (χ^2)	sig.
Demographics												
Age	45	54.76	10.81	55.00	39	40	55.60	11.17	56.50	41	0.35	0.73
Years of Education	45	14.60	2.62	14.00	13	40	15.93	3.20	16.00	10	2.10	0.04
Years in Town	45	38.44	15.02	37.00	55	40	29.77	17.79	24.00	61	-2.44	0.02
Ethnicity											(1.35)	(0.51)
African-American	1	2%				2	5.0%					
Caucasian	43	95.60%				38	95.0%					
Asian-American	1	2%				0	0.0%					
Native American	0	0%				0	0.0%					
Marital Status											(2.44)	(0.65)
Single	2	4%				3	8%					
Married	37	82%				31	78%					
Divorced	5	11%				5	13%					
Widowed	1	2%				0	0%					
Co-habitating	0	0%				1	3%					
Household Income ($ / yr)											(4.33)	(0.93)
0 - 29,999	11	25%				7	18.40%					
30,000 - 59,999	13	29.50%				9	23.70%					
60,000 - 89,999	9	20.50%				13	15.80%					
90,000 and above	11	25%				9	23.70%					
Biomarkers												
Blood Mn (µg/L)	45	8.83	1.87	8.55	7.4	40	9.21	3.21	8.46	13.55	*0.67*	*0.51*
Natural log of Mn	45	2.16	0.22	2.15	0.90	40	2.17	0.32	2.13	1.29	*0.21*	*0.84*
Blood Cd (µg/L)	45	0.50	0.58	0.28	2.73	40	0.43	0.66	0.26	3.92	-0.50	0.62
Blood Hg (µg/L)	45	1.32	2.24	0.74	14.37	40	1.24	1.69	0.79	9.52	-0.18	0.86
Blood Pb (µg/dL)	45	1.85	1.16	1.69	4.97	40	1.58	1.17	1.14	5.39	-1.08	0.29
Serum ferritin (ng/mL)	45	189.62	180.33	129	843.7	40	179.37	131.17	142	546.31	-0.30	0.77
Natural log of Ferritin	45	4.84	0.95	4.86	4.09	40	4.89	0.88	4.95	4.28	0.21	0.83
Hazard Quotient	45	3.72	2.48	3.32	13.29							
CEI	45	6.95	4.93	6.27	31.56							

Table 3. Demographics and biomarkers gender comparison between towns (Females)

		FEMALES											
		Marietta					**Mt Vernon**					**t-tests**	
		n	Mean (%)	SD	Median	Range	n	Mean (%)	SD	Median	Range	t-statistic (χ^2)	sig.
Demographics													
Age		55	54.15	9.10	56.00	42	50	55.48	10.90	55.00	42	0.68	0.50
Years of Education		55	14.51	2.77	14.00	12	50	14.58	2.79	13.50	10	0.13	0.90
Years in Town		55	34.13	16.20	35.00	51	50	36.64	16.34	34.00	64	0.79	0.43
Ethnicity												(2.14)	(0.54)
	African-American	1	2%				0	0.0%					
	Caucasian	50	92.60%				49	98.0%					
	Asian-American	1	2%				0	0.0%					
	Native American	2	4%				1	2.0%					
Marital Status												(4.60)	(0.33)
	Single	4	7%				3	6%					
	Married	44	80%				37	74%					
	Divorced	6	11%				7	14%					
	Widowed	0	0%				3	6%					
	Co-habitating	1	2%				0	0%					
Household Income ($ / yr)												(10.15)	(0.43)
	0 - 29,999	15	31.20%				7	15.20%					
	30,000 - 59,999	15	31.30%				23	50.00%					
	60,000 - 89,999	10	20.80%				6	13.10%					
	90,000 and above	8	16.70%				10	21.70%					
Biomarkers													
Blood Mn (µg/L)		55	10.33	3.88	9.53	19.69	50	9.69	3.14	9.35	15.15	-0.92	0.36
Natural log of Mn		55	2.27	0.34	2.25	1.61	50	2.22	0.33	2.23	1.62	-0.84	0.40
Blood Cd (µg/L)		55	0.56	0.50	0.32	2.22	50	0.51	0.43	0.38	1.80	-0.55	0.58
Blood Hg (µg/L)		55	1.38	1.43	0.83	6.62	50	0.74	0.69	0.53	2.82	*-2.96*	*0.004*
Blood Pb (µg/dL)		55	1.32	0.67	1.11	2.9	50	1.28	0.71	1.16	3.68	-0.36	0.72
Serum ferritin (ng/mL)		55	85.17	107.53	62.50	626.80	50	91.65	72.72	64.45	319.51	0.36	0.72
Natural log of ferritin		55	4.08	0.785	4.14	3.96	50	4.22	0.81	4.17	3.55	0.90	0.37
Hazard Quotient		55	3.66	2.75	3.10	18.40							
CEI		55	6.95	4.93	6.27	31.56							

* Marietta Females had significantly higher Hg levels than Mt Vernon females (t-test)

* *Italics* = equal variances not assumed

Table 4. Symptom categories by town (χ2)				
Symptom Category (Dichotomous)	Mt. Vernon	Marietta	Chi-Square	*p*
neurological	38%	48%	1.84	0.18
musculoskeletal	51%	56%	0.37	0.54
tremor	7%	14%	2.71	0.10
rigidity	2%	8%	3.17	0.08
bradykinesia	22%	26%	0.37	0.54
postural instability	10%	15%	1.07	0.30
other UPDRS Sx	2%	2%	0.01	0.92
UPDRS ADL	20%	22%	0.14	0.71
UPDRS Sx total	37%	43%	0.90	0.34
other motor	19%	34%	5.72	0.02
memory concentration	100%	100%	*	*
anxiety	29%	48%	7.28	0.01
depression	26%	36%	2.41	0.12
visual	12%	23%	3.75	0.05
sensory	13%	20%	1.50	0.22
dermatological	9%	10%	0.07	0.79
gastrointestinal	18%	19%	0.05	0.83
respiratory	39%	45%	0.62	0.43
sexual	17%	16%	0.01	0.93
other Sx	17%	27%	2.94	0.09
sleep	74%	67%	.96	0.33
headache chemicals	100%	100%	*	*

Table 6. Neuropsychological tests by Town

	Mt. Vernon			Marietta			t-tests			ANCOVAs controlling for education level		Mann Whitney test	
	n	Mean	SD	n	Mean	SD	*t*	*p*	effect size[††]	*F*	*p*	z	p
NAB Memory Index Score	90	100.21	14.65	100	100.81	15.84	-0.27	0.79	-0.15	-			
NAB Story Learning Phrase Unit Immed. T Score	90	45.98	9.66	100	45.33	12.41	0.40	0.69	0.20	-			
NAB Story Learning Phrase Unit Delayed T Score	90	48.68	9.14	100	47.11	10.30	1.11	0.27	0.51	-			
NAB Shape Learning Immediate Recognition: T score	90	53.46	8.56	100	53.89	8.61	-0.35	0.73	-0.15	-			
NAB Shape Learning Delayed Recognition: T score	90	52.17	10.02	100	52.26	8.57	-0.07	0.95	-0.03	-		-0.223	0.816
NAB DLM immed	90	53.33	9.55	100	54.92	11.05	-1.05	0.29	-0.50	-			
NAB DLM delay	90	51.38	10.66	100	51.20	9.83	0.12	0.91	0.06	-			
Trails A T score	90	47.14	11.04	100	48.08	9.34	-0.63	0.53	-0.30	-			
Trails B T Score	90	51.14	11.15	100	52.62	10.70	-0.93	0.35	-0.45	-			
Stroop Word T Score	90	46.98	8.96	100	46.67	7.38	0.26	0.80	0.11	0.02	0.88		
Stroop Color T Score	90	45.31	10.26	100	43.75	7.87	1.17	0.25	0.52	1.20	0.28		
Stroop Color/Word T Score	90	49.81	10.37	100	48.32	10.03	1.01	0.32	0.47	0.59	0.44		
Animal Naming Standard Score	90	113.42	17.30	100	110.01	17.17	1.36	0.18	0.83	-			
Auditory Consonant Trigrams 3" z score	90	0.07	1.12	100	-0.17	1.08	1.51	0.13	0.23	1.38	0.24		
Auditory Consonant Trigrams 9" z score	90	-0.34	1.24	100	-0.52	1.27	0.98	0.33	0.16	0.32	0.57		
Auditory Consonant Trigrams 18" z score	90	-0.19	1.10	100	-0.34	1.08	0.94	0.35	0.14	0.20	0.66		
Auditory Consonant Trigrams Mean of 3, 9, 18 z scores	90	-0.15	0.96	100	-0.34	0.95	1.36	0.17	0.19	0.79	0.37		
Rey-Osterrieth Copy Raw Score	89	29.16	4.78	100	29.92	4.87	-1.08	0.28	-0.35	1.99	0.16	-0.18	0.857
Rey-Osterrieth Immediate Recall T Score	89	43.01	14.24	100	42.60	13.47	0.20	0.84	0.11	0.08	0.77	-0.66	0.509
Rey-Osterrieth Delayed Recall T Score	89	43.10	14.08	100	41.48	12.71	0.83	0.41	0.45	0.12	0.73		
WAIS III Digit Symbol Coding Scaled Score	90	11.14	3.20	100	10.98	3.28	0.35	0.73	0.09	0.01	0.94		
WAIS III Similarities Scaled Score	90	11.20	2.66	100	10.80	3.05	0.96	0.34	0.24	0.01	0.92		
WAIS III Digit Span Total Scaled Score	90	10.59	3.02	100	10.61	2.77	-0.05	0.96	-0.01	0.33	0.57		

TABLE SUMMARY

There are no significant differences between the towns on neuropsychological tests

Table 7. Diet Mn and Fe by town						
	Marietta			Mt Vernon		
Foods	Mean Servings	Mean Mn	Mean Fe	Mean Servings	Mean Mn	Mean Fe
Beef and Poultry	5.72 (4.42)	0.07 (.06)	9.62 (8.27)	6.11 (4.304)	0.08 (.061)	9.49 (6.79)
Seafood	0.87 (1.33)	0.07 (.14)	1.03 (1.98)	0.95 (1.21)	0.05 (.14)	0.97 (1.48)
Vegetables	3.94 (2.43)	1.50 (1.26)	9.88 (6.22)	4.5 (2.94)	1.76 (1.43)	10.88 (7.58)
Fruits	1.49 (2.91)	0.61 (1.03)	0.95 (1.93)	2.23 (4.13)	0.94 (1.43)	1.43 (2.78)
Soy Products	0.15 (.73)	0.11 (.45)	0.47(1.87)	0.18 (.62)	0.18 (.68)	1.00 (4.03)
Grains	5.16 (6.25)	10.26 (13.04)	19.75 (26.60)	5.44 (5.46)	10.42 (11)	19.24 (22.41)
Nuts, Seeds and Legumes	4.40 (5.36)	2.96 (3.78)	5.58 (9.38)	5.52 (5.69)	3.69 (3.71)	6.61 (6.82)
Beverages	8.07 (12.75)	3.14 (4.99)	0.72 (1.18)	7.95 (11.26)	3.06 (4.35)	1.09 (1.63)
TOTAL	29.22 (19.37)	18.20 (15.68)	45.06 (31.40)	32.81 (18.96)	19.69 (14.73)	47.25 (30.08)
* Independent sample t-test did not find any differences between the exposed town and the control town.						

Figures:

Figure 1
Recruitment letters and calls - Marietta

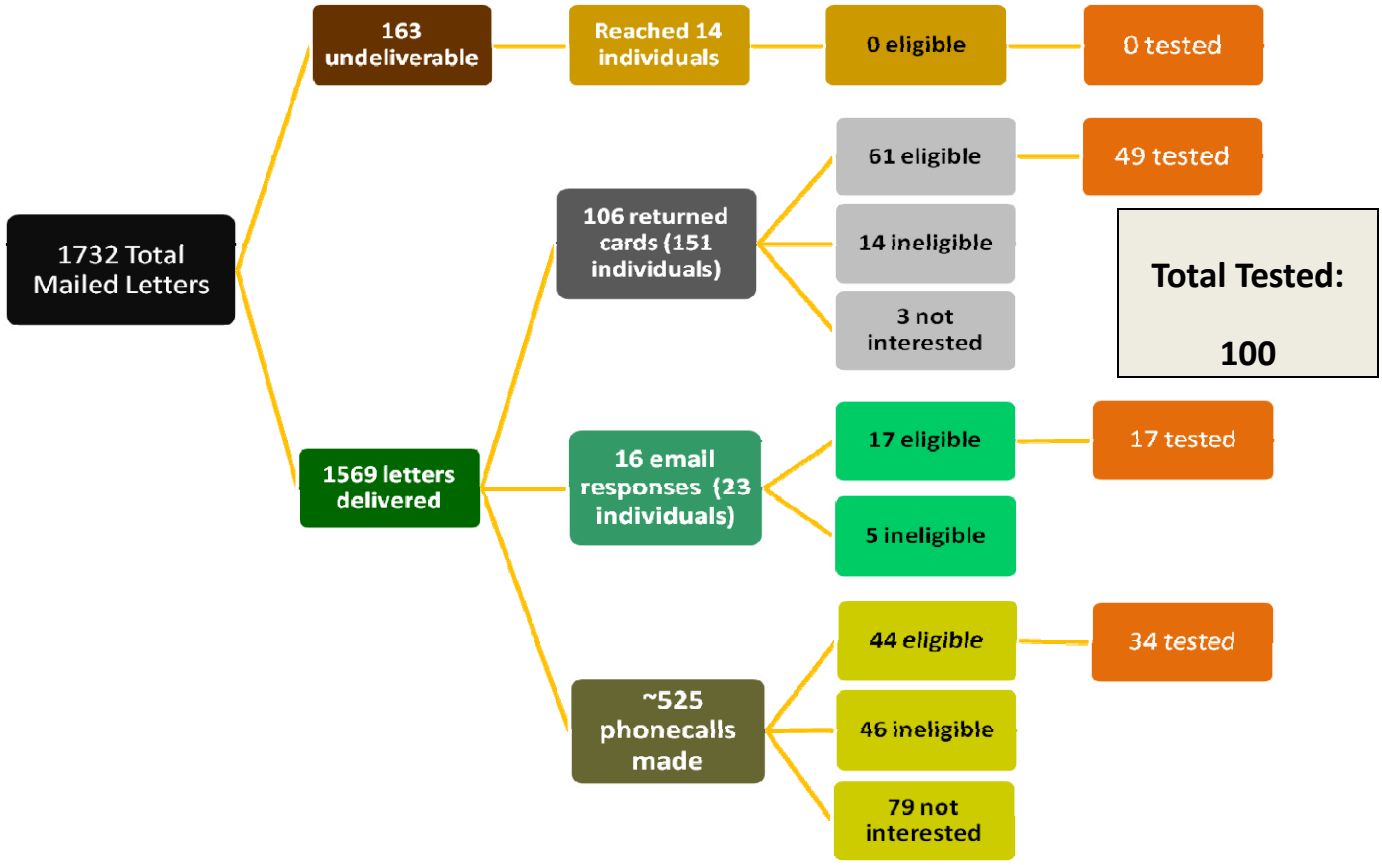
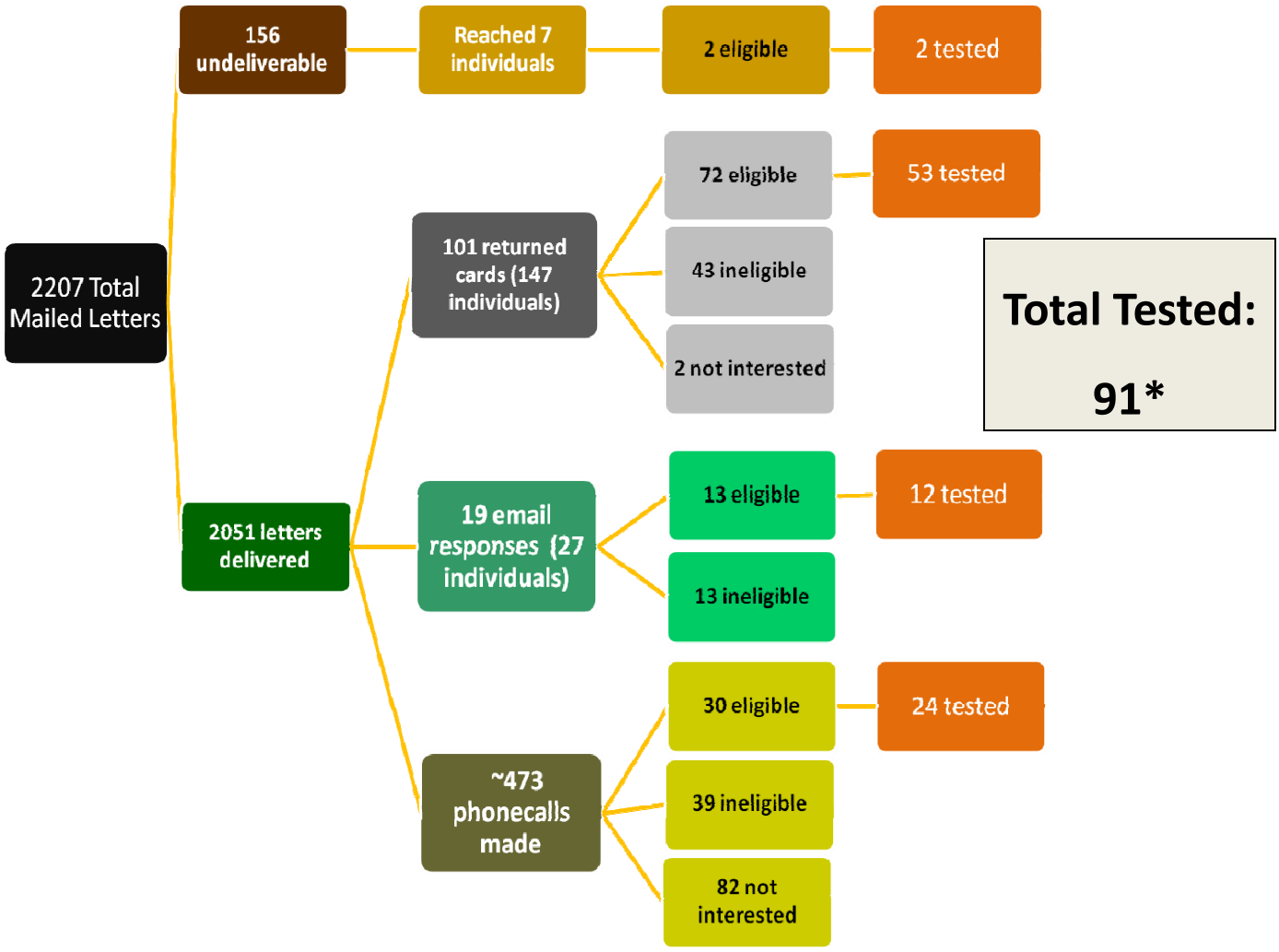
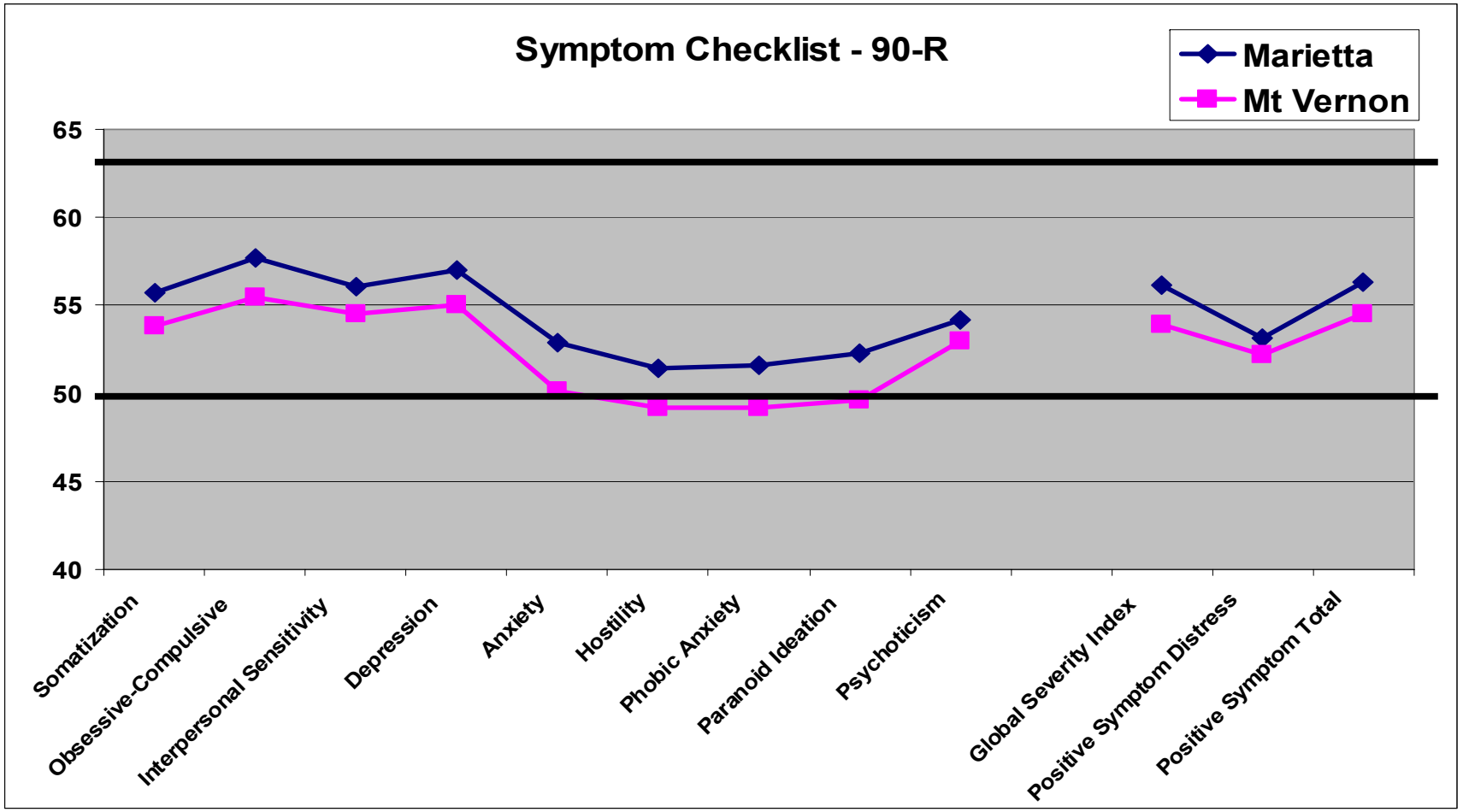


Figure 2
Recruitment letters and calls – Mount Vernon



** 1 person excluded post-testing due to insufficient years of residency*

Figure 3
SCL-90-R T scores by town



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Kim, Y., Bowler, R.M., Abdelouahab, N., Harris, M., Gocheva, V., Roels, H.A., 2011. Motor function in adults of an Ohio community with environmental manganese exposure. Neurotoxicology. 32**,** 606-614.

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Appendix A

Methodological aspects of an epidemiologic study of adults living near a Mn point source*

Rosemarie M. Bowler[1], Y. Kim[2], L. Ngo[3], and H.A Roels[4]

[1]San Francisco State University, San Francisco, CA, [2]Ulsan University Hospital, Ulsan, S Korea, [3]Harvard Medical School, Boston, MA, [4]Université catholique de Louvain, Brussels, Belgium

Background: Exposure to high levels of Mn in occupational studies showed health effects similar to Parkinson's Disease, with neurological and neuropsychological sequelae. Few adult residential studies of Mn exposure report air dispersion modeling, biomarkers, neurological and neuropsychological test results.

Methods: This multidisciplinary epidemiologic study used a recruitment strategy utilizing property tax and water records for random selection of 200 residents out of ~3939 in both a Mn-exposed and control town. Standardized tests of attention, immediate and delayed memory, cognitive flexibility, emotional function, and the UPDRS ADL and motor scales were studied with regard to biomarkers, Mn in air, scales of symptoms and illnesses, and dietary intake of Mn and Fe.

Results: Preliminary results show a positive relationship between the neurological UPDRS motor and the neuropsychological tests of Fingertapping, Grooved Pegboard, Dynamometer and parallel lines tremor test.

Conclusion: Neurological and neuropsychological methods correlate significantly, suggesting that several of the functional tests can be used interchangeably. Environmental Mn exposures are significantly lower than occupational exposures –likely posing a lower risk for clinical illness than occupationally inhaled Mn.

**Submitted to the 26th International Neurotoxicology Conference, Portland, Oregon June 6-10, 2010, This study was funded by the U.S. EPA under Co-op. Agreement P8341600*

Appendix B

RELATIONSHIPS BETWEEN MOOD AND NEUROPSYCHOLOGICAL PERFORMANCE IN ADULTS WITH ENVIRONMENTAL EXPOSURE TO MANGANESE

Harris, M[1].; Bowler, R[2].
[1]Alliant International University, San Francisco, CA [2]San Francisco State University

Background: Manganese (Mn) classified as a neurotoxin affecting brain function (ATSDR, 2000), which can include motor disturbances similar to those found in Parkinson's Disease (Roels et al., 1992), neuro-cognitive effects (Mergler et al., 1994), and mood disturbance (Bowler et al., 2007). Cognitive functioning and motor performance can also be adversely affected by emotional disturbance, particularly anxiety and depression (Lezak, 2004). **Methods:** Adult participants (N=100) were randomly selected from Marietta, OH, which houses the largest Mn-producing plant in the US (EPA, 2004). Participants completed the Symptom Checklist 90-Revised and a battery of neuropsychological tests. Principal components analysis derived seven factors: *Recall Memory, Working Memory, Information Processing/Speed, Trail Making, Grip Strength, Motor Speed*, and *Complex Motor Dexterity*. **Results:** Adjusting for age, gender, and education, Depression was negatively related to Trail Making (β= -.218, *p*=0.030), Working Memory (β = -.197, *p* = .035), Information Processing/Speed (β= -.260, *p*=0.008), Motor Speed (β= -.249, *p*=0.019), and Complex Motor Dexterity (β = -.216, *p* = .039), while Anxiety was negatively related to Trail Making (β = -.310, *p* = .002), Information Processing/Speed (β= -.274, *p*=0.006), Motor Speed (β= -.288, *p*=0.007) and Complex Motor Dexterity (β= -.224, *p*= 0.034). Neither mood variable was related to Recall Memory or Grip Strength. Living proximity to the Mn-producing plant was negatively related to Information Processing/Speed and Trail Making, and positively related to Anxiety. Interaction effects between plant proximity and mood were found for Trail Making. **Conclusion:** Mood has a moderate negative impact on neuropsychological functioning in several domains, especially cognitive flexibility, motor speed, and information processing speed. This relationship may be stronger with higher exposure to Mn, and should be considered when examining the neuropsychological effects of exposure to neurotoxins.

Acknowledgement: *This study was funded by the U.S. EPA under Co-op. Agreement P8341600*

Appendix C

Health Study of Manganese Exposure of Adults in Marietta & Mt. Vernon, Ohio: Preliminary Results

Rosemarie M. Bowler, Ph.D., M.P.H.
San Francisco State University

Marietta, Ohio
June 24, 2010

1

Funding by: U.S. Environmental Protection Agency (EPA), Cooperative Agreement # 83416001-0

USEPA Project Officer: Dr. Danelle Lobdell, epidemiologist, National Health and Environmental Effects Research Laboratory
USEPA Region 5 Contact: Dr. George Bollweg

2

Collaborators

- Dr. Harry Roels – Belgium, Professor emeritus at Catholic University at Louvain
- Dr. Long Ngo – Assistant Professor of Medicine in Biostatistics at Harvard Medical School
- Ms. Stephanie Davis – ATSDR
- ATSDR provided scientific support and assisted in mailing recruitment letters
- Dr. Nadia Abdelouahab – Montreal, Canada – University of Quebec at Montreal
- Dr. Yangho Kim – Physician at Ulsan University, South Korea, experienced in assessing workers exposed to manganese
- Ms. Jaime Wagner - U.S. Environmental Protection Agency, Region 5
- Dr. Alan Ducatman – Professor and Chair of West Virginia University, Dep. of Community Medicine
- Dr. Donna Mergler – Montreal, Canada - Professor Emerita, University of Quebec at Montreal
- 2 neuropsychologists and 6 advanced doctoral and masters graduate students experienced and trained in the methods used in the study

3

Advisory Board

- Dr. Kathleen Meckstroth, Health Commissioner, Washington County Health Department, Marietta
- Dr. Michael Brockett, Health Commissioner of Marietta, City Health Department
- Mr. Michael Mullen, Mayor of Marietta
- Mr. Richard Mavis, Mayor of Mt. Vernon
- Health Scientists from ODH – Dr. Forrest Smith, Dr. Bob Frey, Mr. Greg Stein
- ATSDR – Dr. Mark Johnson and Dr. Michelle Colledge
- CDC – Div. Of Laboratory Sciences – Dr. Kathleen Caldwell
- Mr. Dennis Murray, Health Commissioner, Knox County Health Department, Mt. Vernon, Ohio
- 2 Marietta Community members: Dr. Eric Fitch & Dr. Diane Dudzinski

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Outline

I. Study Overview

II. Results
- A) Recruitment
- B) Demographics
- C) Air dispersion modeling
- D) Blood Analyses
- E) Neuropsychological testing
- F) Mood
- G) Health, Illnesses and Symptoms
- H) Neurological Examination
- I) Mn Intake in Diet

III. Brief summary & appreciation to Participants & Study

IV. Q & A

About the Study

- A community environmental epidemiologic study
- 1st comprehensive environmental study of Mn exposed adults in the U.S.
- Includes air monitoring, biomarkers, health, neuropsychological, neurological and sensory assessments.
- Extensively reviewed and approved by:
  - U.S.EPA
  - Ohio Department of Health
  - San Francisco State University

5

Goals of this Research

- To begin to address Marietta residents' health concerns about airborne manganese (Mn) exposure
- To evaluate potential exposure to and health effects of airborne Mn in adult residents
- To help evaluate current health guidelines for airborne Mn
- To evaluate tests used in workplace studies for use in residential studies
- To evaluate relationships among blood Mn (MnB) and airborne Mn (MnA) and health and function

7

Requirements for Participation

- Randomly selected Marietta and Mount Vernon residents (from a property tax parcel map and water department records)
- Having lived in Marietta or Mount Vernon for 10 or more years
- Age: 30-75 years
- Up to 2 eligible members from a selected household

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Exclusion Criteria

- Having worked at the former Union Carbide Complex
- Having lived in Marietta (for Mt Vernon residents only)
- Being pregnant or breastfeeding
- Exposure to pesticides, fungicides, herbicides, CO, other metals requiring a doctor visit
- Head injury
- Stroke
- Electroconvulsive treatment
- Epilepsy
- Brain surgery
- Encephalitis
- Meningitis
- Multiple sclerosis
- Parkinson's disease
- Huntington's chorea
- Alzheimer's dementia
- Schizophrenia
- Bipolar disorder
- Current treatment for alcohol or drug dependence

Data We Collected

- Questionnaires:
  - Residency
  - General Health
  - Sleep
  - Mood
  - Diet
  - Symptoms, Illnesses, and Medication use

- Medical & Neuropsychological Evaluations
  - Neurological
  - Small Blood Sample
  - Clinical Interview by P.I.

- Neurobehavioral Tests
  - Cognitive Testing
  - Motor Testing
  - Mood Testing
  - Postural Sway & Tremor Testing

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Medical Evaluations

- Blood sample
  - Analyzed at the CDC National Laboratory for levels of manganese, cadmium, lead, and mercury. Serum (part of plasma, which is part of blood) was analyzed for levels of ferritin – indicating amount of iron stored in your body
- Neurological
  - A brief medical evaluation by Dr. Yangho Kim, experienced in assessing manganese exposed workers; included examination of speech, swallowing, balance, gait, tremors and activities of daily living
- Neuropsychological
  - A brief clinical interview with the P.I. about general health and psychological status

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Maintaining Confidentiality

- All information combined in group results
- Personal information confidential, available to the participant ONLY
- Individual identification number (ID) assigned
- No names (only ID numbers) on all tests or questionnaires
- Only the P.I. has the list that links names and IDs

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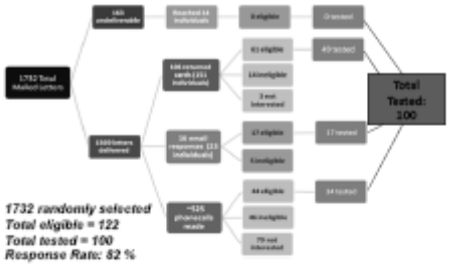
Results: Recruitment

Results of Recruitment: Marietta



1732 randomly selected
Total eligible = 122
Total tested = 100
Response Rate: 82 %

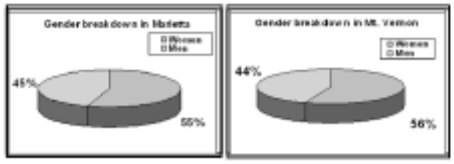
Results of Recruitment: Mt. Vernon

2207 randomly selected
Total eligible = 117
*Total tested = 91**
*Response Rate: 78%**

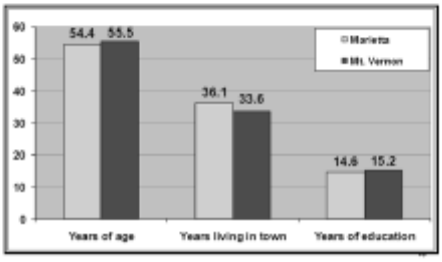
** 1 person excluded post-testing due to insufficient years of residency*

Results: Participant Demographics

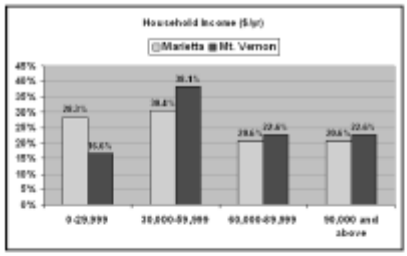
Demographics: Gender



Demographics: Average Years of Age, Residency, & Education



Demographics: Household Income (% of people in each income group)



Air dispersion modeling and cumulative exposure index

Why was modeling performed?

- U.S. EPA Region 5 was asked to perform air dispersion modeling in support of this health study*.
- Models can estimate air quality—in this case, manganese concentrations—in the vicinity of a source
- Results allowed researchers to develop a Cumulative Exposure Index (CEI):
  modeled ambient air-Mn (µg/m³) × years of residency
- Model used: EPA's AERMOD modeling system.

*U.S. EPA made no conclusions or recommendations—merely provided modeling results.

What information is required for modeling?

- Meteorological Data
  - Winds speed, wind direction, precipitation, etc.
  - Met data obtained from nearby National Weather Service stations.
- Emissions information
  - Amount of pollutant emitted
  - Release characteristics (location, height of the stack, how fast the pollutant is coming out of the stack, the temperature of the release, etc.)
- Receptors
  - You have to tell the model where you want it to calculate concentrations; these locations are called "receptors," which are the distance from the source
- *Using this information, the model will predict manganese concentrations in the air at the locations of interest.*

What do we compare the modeling results to?

- Modeled concentrations of Mn can be compared to the *Mn reference concentration (RfC)*.
- **The RfC is the concentration of a pollutant in the air at which we would not expect to see any harmful effects if breathed for a lifetime .**
  - Lifetime exposure is assumed to be 24 hours a day for 70 years.
- **The ratio of modeled Mn concentration to RfC is known as the *hazard quotient* (HQ). An HQ less than or equal to 1.0 is generally not of concern.**
  - If the predicted concentration is less than or equal to the RfC, we expect no harmful effects.
- For manganese, the RfC is 0.05 µg/m³ (micrograms per cubic meter).

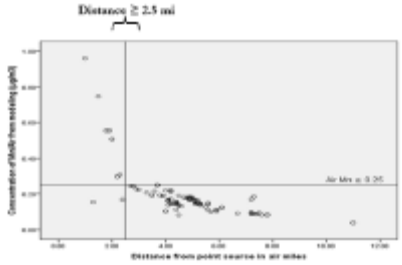
Dispersion Modeling, Hazard Quotient, and CEI: Uncertainties

- **Annual Mn emission rate (tons per year) assumed to be emitted equally in grams per second over an entire year**
- **Assume that people breathe the modeled concentration 24 hours a day, 365 days a year over a 70-year lifetime.**
- **Exposure indicators, not measurements**
- **Do not include human activity patterns or other important variables**
- **Do not take into account changes in emissions over time**

Results

	Average	Minimum	Maximum
Modeled Mn in air (µg/m³) of 100 receptors	.18	.04	.96
Hazard Quotient (Modeled Mn divided by the ref. concentration of 0.05 µg/m³)	3.69	.77	19.17
Cumulative Exposure Index (CEI) (Modeled Mn in air x years of residency in Marietta)	6.67	.89	41.22

Distance from point source and Air Mn



Greater distance from the source was related to lower concentration of Air Mn

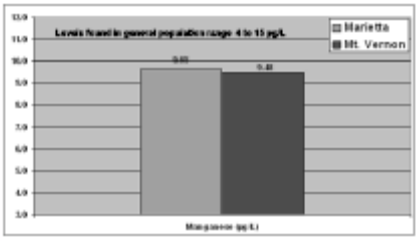
Results: Blood Analyses

Manganese

- Some manganese is always found in the body, because it is essential for normal function
- Excess manganese is usually removed from the body within a few days → difficult to measure past exposures

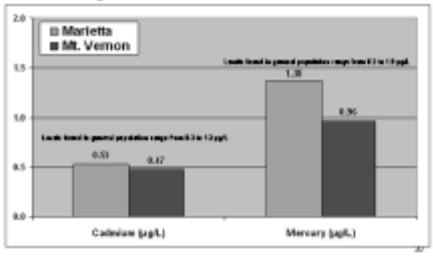
Manganese

No significant difference between the towns



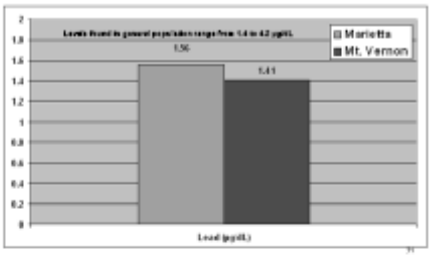
Cadmium and Mercury

No significant difference between the towns



Lead

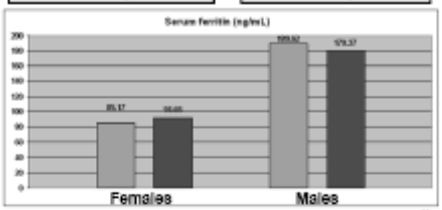
No significant difference between the towns



Serum Ferritin

No significant difference between the towns

As expected, women have lower iron stores than men-both towns



Preliminary Results for Neuropsychological Testing between Marietta and Mt. Vernon

Tests of Effort

- All but one participant from Mt. Vernon passed the test of effort
- The participant who did not pass was given a more sensitive test of effort, which he/she passed, clearly indicating validity of test performance

No significant difference between the towns on:

- Motor speed
- Motor strength and tremor
- Attention and immediate memory
- Switching categories and divided attention
- Visual delayed memory
- Verbal delayed memory

Scores in both towns were within the average (normal) range

Relationship between Exposure and Neuropsychological Tests

- Mn in blood:
  - Overall, we did not observe a consistent relationship between levels of Mn in blood and performance on the neurobehavioral tests (in both Marietta and Mt. Vernon)
- Hazard Quotient (modeled Mn in air divided by the reference value)
  - Higher HQ was related to worse performance on some tests (HQ only calculated for Marietta; HQ is related to distance from the source)
- CEI (modeled Mn in air X years of residency)
  - Higher CEI was related to worse performance on some tests (CEI only calculated for Marietta; also related to distance from the source)

Hazard Quotient

- Higher HQ was related to worse performance on
  - 3 tests of visual memory and one of category naming
- Those with higher HQ tended to score lower on
  - Shape learning immediate
  - Animal Naming
  - Rey-O immediate
  - Rey-O delayed

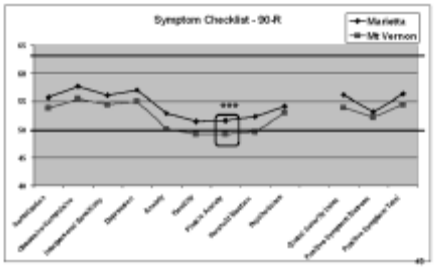
Cumulative Exposure Index (CEI)

Higher CEI was related to worse performance on:

- Animal Naming
- Digit Symbol Coding

Results: Mood

No significant difference between the towns, except for phobic anxiety being higher in Marietta.



Relationship between Exposure and Mood

- Manganese in blood:
  - Overall, we did not observe a consistent relationship b/n levels of Mn in blood and scores on the mood questionnaires
- Hazard Quotient (modeled Mn in air divided by the reference value)
  - Higher HQ was related to higher phobic anxiety
- CEI (modeled Mn in air x years of residency)
  - Higher CEI was related to more depression, more anxiety, more hostility, more phobic anxiety, more paranoid ideation, more psychoticism, higher global severity index score, more positive symptoms total

Results: Health, Illnesses and Symptoms between Marietta and Mt. Vernon

No significant difference between the towns on:

- Percent of people reporting poor or fair health
- Average number of poor physical health days in a month
- Average number of poor mental health days in a month
- Percent of adult smokers
- Prevalence of adult obesity (based on body fat as measured by height divided by weight)

Individual self-reported symptoms significantly different between the towns

Sensory Symptoms & Headaches

	Marietta	Mt. Vernon
Changes in sense of smell	14 %	4.4%
Changes in sense of taste	10%	0%
Headaches (1x/week or more)	24%	11.1%
Headaches (presence of pain)	13.1%	4.4%
Headaches (presence of pain)	22%	6.8%

Parkinsonism Symptoms

	Marietta	Mt. Vernon
Tightness of facial muscle	5.1%	1.1%

Emotional Symptoms

	Marietta	Mt. Vernon
Feeling anxious	34%	20%
Feeling irritable	39%	17.8%
Change in personality	14%	2.2%

Individual self-reported symptoms significantly different between the two towns

Other symptoms

	Marietta	Mt. Vernon
Excessive perspiration	17%	5.6%
Fever or Chills	8%	0%
Nausea (not food-related)	12%	3.3%

Illnesses

Illness Category	Marietta	Mt. Vernon	Sig.
neoplasms	10%	10%	ns
emotional	12.2%	10%	ns
eye	14%	21.1%	ns
digestive	4%	4.4%	ns
blood	10.1%	9%	ns
endocrine	23.2%	15.6%	ns
diabetes	13%	11%	ns
nervous system	2%	1.1%	ns
skin	21%	25.5%	ns
genitourinary	19%	27.8%	ns
injury	4%	4.4%	ns
circulatory	37.8%	43.3%	ns
respiratory	66.7%	67.4%	ns
pneumonia	14%	27.8%	sig
musculoskeletal	46.4%	38.2%	ns
other	11%	12.2%	ns

Relationship between Exposure, Illnesses, and Symptoms

- Manganese in blood:
  - Related to more frequent occurrence of endocrine (e.g. diabetes) and psychological illness in Marietta
  - Related to more frequent reporting of rigidity (stiffness) in the whole group (Marietta + Mt Vernon)
- Hazard Quotient (modeled Mn in air divided by the reference value)
  - No consistent relationships observed with diagnosed illnesses
- CEI (modeled Mn in air x years of residency)
  - No consistent relationships observed with illnesses or symptoms
  - Medication analysis is in progress

Results: Neurological Examination

Movement

- Examination with the Unified Parkinson's Disease Rating Scale (UPDRS)
- Marietta participants had slower movement (bradykinesia) and motor speed than Mt. Vernon participants on one subtest
- No statistical Mn relationship between exposure variables (blood Mn, modeled Mn in air, HQ, and CEI) and movement (variables not available for Mt. Vernon)

Results: Mn Intake in Diet

Average Daily Intake of Dietary Mn

Average Dietary Consumption of Manganese: General Population*
0.7-10.9 (mg/day)

Average daily intake by Category	Marietta		Mt Vernon	
	Males	Females	Males	Females
Total (mg/day)	2.33	2.82	2.73	2.88

No significant difference between the towns

Summary

Summary of Findings

- Significant differences between towns on the following:
  - Participants in Marietta reported significantly more symptoms
  - Marietta participants had more slowness in movement than Mt. Vernon participants
- Mn in blood
  - Related to more frequent occurrence of diabetes and psychiatric illness in Marietta
  - Related to more frequent reporting of rigidity (stiffness) in both towns
- HQ
  - Higher HQ was related to:
    - Worse performance on tests of executive functioning
    - Higher phobic anxiety
    - More frequent reporting of excessive perspiration
    - No consistent relationships observed with illnesses
- CEI
  - Higher CEI was related to:
    - Worse performance on some neuropsychological tests
    - Endorsement of anxiety and paranoia
    - No consistent relationships observed with illnesses or symptoms

Conclusions

- Overall, results of this epidemiologic study using random sampling, did not support findings of clear-cut adverse health effects from Mn in air and blood in the town of Marietta
- This is supported by the lack of differences between Marietta and Mt Vernon on neuropsychological tests
- Marietta participants had more symptoms, slower movement than in Mt. Vernon
- Those residing close to the point source did slightly worse on some neuropsychological tests than other participants in Marietta
- Overall test results are within the average range of the general population

Appendix D

Relationship of residential airborne manganese exposure to neuropsychological, neurological and health status of adults

Rosemarie Bowler, Ph.D., M.P.H.
San Francisco State University

Ohio Department of Health
Columbus, Ohio
June 24th, 2010

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Funding: U.S. Environmental Protection Agency (EPA), Cooperative Agreement # 83416001-0

USEPA Project Officer: Dr. Danelle Lobdell, epidemiologist, National Health and Environmental Effects Research Laboratory

USEPA Region 5 Contact: Dr. George Bollweg

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Outline

- Study Team
- EPA Manganese Study
- Test Battery description and examples
- Recruitment process and outcomes
- Results:
  - Participant Demographics
  - Air Modeling – Jamie Wagner
  - Blood Analyses – Harry Roels
  - Neuropsychological Testing
  - Mood
  - Health, Illnesses, and Symptoms
  - Movement and Tremor
- Summary
- Q & A

3

Study Collaborators

- Dr. Harry Roels – Brussels, Belgium – Professor emeritus, Université catholique de Louvain
- Dr. Long Ngo – Assistant Professor of Medicine in Biostatistics at Harvard Medical School
- Ms. Stephanie Davis – ATSDR provided samples and exposure information
- ATSDR provided scientific support and assisted in mailing recruitment letters
- Dr. Nadia Abdelouahab – Montreal, Canada – University of Quebec at Montreal
- Dr. Yangho Kim – Physician at Ulsan University, South Korea, expert in assessing workers exposed to manganese
- Ms. Jaime Wagner - U.S. Environmental Protection Agency, Region 5
- Dr. Alan Ducatman – Professor and Chair of West Virginia University, Dep. of Community Medicine
- Dr. Donna Mergler – Montreal, Canada – Professor emerita, University of Quebec at Montreal
- 2 neuropsychologists, Ms. Vilma Gochera, manager and assistant responsible for assistance in slide creation and 6 advanced doctoral and masters graduate students experienced and trained in the methods used in the study

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Advisory Board

- Dr. Kathleen Meckstroth, Health Commissioner, Washington County Health Department, Marietta
- Dr. Michael Brockett, Health Commissioner of Marietta, City Health Department
- Mr. Michael Mullen, Mayor of Marietta
- Mr. Richard Marin, Mayor of Mt. Vernon
- Health Scientists from ODH – Dr. Forrest Smith, Dr. Bob Frey, Mr. Greg Stein
- ATSDR – Dr. Mark Johnson and Dr. Michelle Colledge
- CDC – Div. of Laboratory Sciences – Dr. Kathleen Caldwell
- Mr. Dennis Murray, Health Commissioner, Knox County Health Department, Mt. Vernon, Ohio
- 2 Marietta Community members: Dr. Eric Fitch & Dr. Diane Dudzinski

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EPA Manganese Study: Aims-Motivation-Exposure Design-Population Recruitment

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Study Aims

Overall, the study aimed to address 2 questions:

1. Do neurological and neuropsychological functions in a group of adults environmentally exposed to Mn, differ significantly from that of a demographically similar group without known ambient air Mn exposure?

2. Is there a relationship between Mn levels in blood (internal dose) or Mn levels in ambient air (external exposure) and neurological /neurobehavioral functions in adults?

The study is funded as a co-operative agreement with the EPA and may serves as a large pilot project for a proposed larger ATSDR study at a future date.

7

Literature Background

- Most Mn studies examined high-level exposures (air) in occupational settings:
  - * Roels et al. (1987, 1992, 1999)
  - * Iregren et al. (1994)
  - * Mergler et al. (1994)
  - * Lucchini et al. (1995, 1999)
  - * Sjögren et al. (1996)
  - * Bast-Petersen et al. (2004)
  - * Kim et al. (2005)
  - * Bowler et al. (2007)
- Limited reports on environmental Mn exposures, all from outside US, focusing on Mn in:

drinking water	ambient air
* Zhang et al. (1995) **(China)**	* Mergler et al. (1999) **(Canada)**
* Wasserman et al. (2006) **(Bangladesh)**	* Finkelstein et al. (2007) **(Canada)**
* Bouchard et al. (2007) **(Canada)**	* Lucchini et al. (2007) **(Italy)**

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Motivation for the Study

- Elevated air Mn emissions (3-4 × the RfC) from the last active Mn smelter in the U.S., Marietta, OH
- Community has requested a study for nearly a decade
- USEPA funding of study proposal
- Collaboration with Ohio Department of Health and Health Commissioners
- Collaboration with ATSDR

- 1st comprehensive environmental study of residential airborne Mn in the U.S. to include air monitoring, biomarkers, health, neurological and neuropsychological assessments.

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Marietta Exposure Source

- Eramet Marietta Inc. (EMI) is a major producer of Mn ferroalloys and one of the largest Mn smelters worldwide.

- EMI ranks 1st in total air release of Mn among all US facilities reporting to the USEPA Toxic Release Inventory (TRI)
- 5 air monitors in Marietta region: 1st in 2000; 2nd in 2004; 3 more for ambient air monitoring (April 2007 to March 2008)

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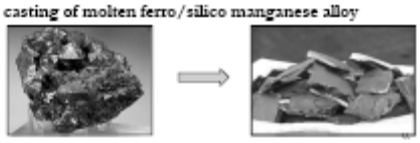
From manganese to Mn-alloy

- Elemental Mn: at.number 25, at.wt 54.94
  a gray-white metal resembling iron,
  but harder, more brittle, insoluble in water
- Melting point 1564°C
- Mn-containing fume is generated in the pouring and casting of molten ferro/silico manganese alloy



Occupational exposure limits for Mn

Workers (total dust): 8-h workday and 40-h workweek			
ACGIH	TLV-TWA	200 µg/m³	0.2 mg/m³
NIOSH	REL	1000 µg/m³	1.0 mg/m³
OSHA	PEL (ceiling)	5000 µg/m³	5.0 mg/m³

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Residential exposure limits for Mn in air

General Population: (PM10, particulate matter ≤ 10 μm) 24 hrs per day for a duration of 75 years			
ATSDR	MRL	0.04 μg/m³	0.00004 mg/m³
USEPA	RfC	0.05 μg/m³	0.00005 mg/m³

Results of April 2007-March 2008 Additional Air monitoring and subsequent modeling of air-Mn

Study Design

- Epidemiologic cross-sectional control/exposed design (study area chosen according to air monitoring results of Mn during 2007-2008)
- 100 Mn-exposed and 100 control (minimally-exposed) adults chosen AT RANDOM
- Exposed town – Marietta, Ohio
- Control town – Mt. Vernon, Ohio

Study Population

- Residents between 30 – 75 years of age
- Approximately equal numbers in each town
- Approximately equal numbers by gender
- Distribution of selected residences within certain Mn-air exposure areas

Census Characteristics of the 2 Towns

Inclusion & Exclusion Criteria

Inclusion Criteria

- 30 - 75 years old
- At least 10 year residency in the respective town
- Reside in area with 45750 zip code (Marietta only)
- Up to 2 eligible members from selected households

Exclusion Criteria

- Currently pregnant or breastfeeding
- Major occupational exposure to pesticides, fungicides, CO, or heavy metals requiring a doctor's visit
- Diagnosis of psychiatric, neurological, or hepatic medical condition
- Current treatment for alcohol or drug dependence
- Head injury or stroke with hospitalization for more than 1 day
- Having worked at any time at Ennmet or the previous Union Carbide complex
- Having lived in Marietta (for Mt Vernon only)

Recruitment: Marietta

- Addresses from Property Tax parcels geocoded by residential addresses in a Geographic Information System (GIS)
- Random selection of parcels
- Random selection of a unit within multiple unit residences
- Water department records and white pages reverse lookup to obtain names
- Invitation letter mailed out with stamped return postcards of intent to participate in study
- Follow-up by telephone (including a brief screening call)

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Recruitment: Mt. Vernon

- Random selection of parcels from Property Tax records
- Random selection of a unit within multiple unit residences
- Water department records and white pages reverse lookup to obtain names
- Invitation letter mailed out with stamped return postcards of intent to participate in study
- Follow-up by telephone (including a brief screening call)
- Recruitment until needed

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Contact Materials Examples

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Study Procedures

- IRB Consent administered and signed
- Health, medication, illness, symptom, diet and sleep questionnaire
- Mood tests
- Brief interview with PI
- Neuropsychological and neurological testing
- Motor and tremor testing
- Blood sample
- Protocol review before $ 50.00 gift card and check-out
- Feedback Letter reporting results by domain of function (within normal range, outside of normal range)

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Test Battery Description

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Test Battery by domain

Domain	Function	Test
Motor & Tremor	Motor & Psychomotor Speed	Finger Tapping Trails A WAIS III Digit Symbol Coding
	Strength, tactile, and tremor	Dynamometer Grooved Pegboard Purdue Pegs
	Hand Tremor	CATSYS - Tremor
	Sway	CATSYS - Postural Stability Accelerometer Tyrosyn, eyes closed, no foam, firm
Cognitive	Attention & Immediate Memory	WAIS III Digit Span WMS Visual Rev Immediate Recall WMS Shapes Learning Immediate Recall WMS Story Learning Theme Immediate
	Delayed Visual Memory	Rey-O Delayed Recall WMS Shapes Learning Delayed Recall
	Delayed Verbal Memory	WMS Visual Rev Delayed Recall WMS Story Person Delayed Recall WMS Daily Living Recognition
	Cognitive Flexib Sty & Divided attention	Stroop Color Word Trails B Auditory Consonant Trigrams
	Verbal Function	Animal Naming WAIS III Similarities
	Effort	Rey 15 Item test Victoria Symptom Validity Test (if needed)

Test Battery: Questionnaires

Areas of interest	Questionnaire
Residential and exposure history General background information	Health Study Questionnaire
General Psychiatric Symptoms	SCL-90-R Symptom Checklist Environmental Worry (EW)
Movement Disorder Symptoms	Health Study Questionnaire (symptoms section)
Health and satisfaction with life	SF-36 Satisfaction with Life
Male & Female issues in Disc	Health Study Questionnaire (disc section)
Sleep problems	Health Study Questionnaire (sleep section)
Motivation use	Health Study Questionnaire (medication section)
History of medical conditions	Health Study Questionnaire (illnesses section)

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Neurological Examination

- Unified Parkinson's Disease Rating Scale (UPDRS)

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Recruitment Outcomes

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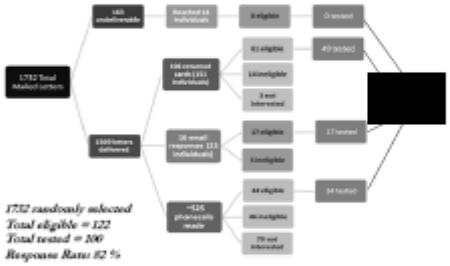
Results of Recruitment: Marietta



1702 randomly selected
Total eligible = 122
Total tested = 100
Response Rate: 82 %

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Results of Recruitment: Mt. Vernon

2207 randomly selected
Total eligible = 117
*Total tested = 93**
*Response Rate: 78%**

**1 person excluded post-scoring due to insufficient years of residency*

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Results:
Participant Demographics

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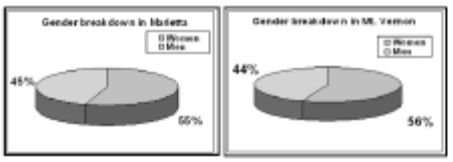
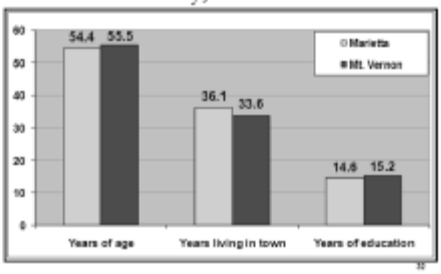
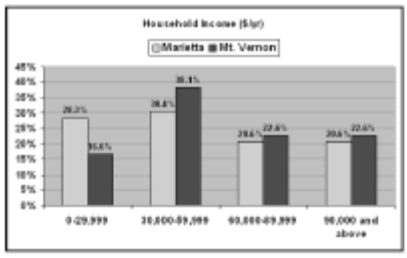
Demographics: Gender



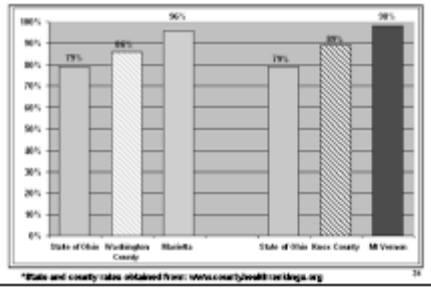
Demographics: Average Years of Age, Residency, & Education



Demographics: Household Income (% of people in each income group)

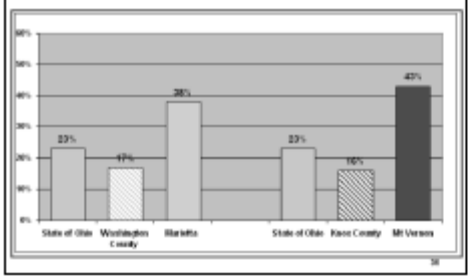


Demographics: Percent of High School Graduates in State, County, & Study Group

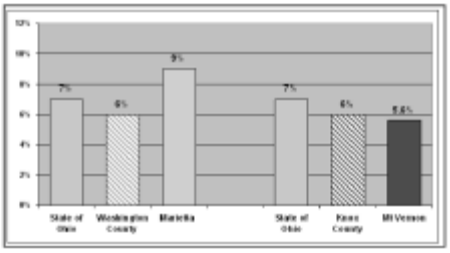


*State and county rates obtained from: www.countyhealthrankings.org

Demographics: Percent of College Graduates in State, County, & Study Group



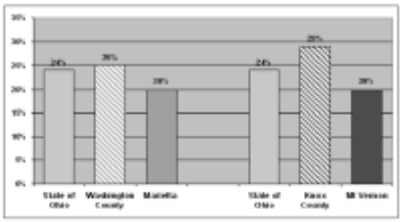
Demographics: Percent of Unemployed in State, County, & Study Group (as of August, 2009)



State and county rates obtained from: www.countyhealthrankings.org

Percent of Adult Smokers

No significant difference between the towns



State and county rates obtained from: www.countyhealthrankings.org

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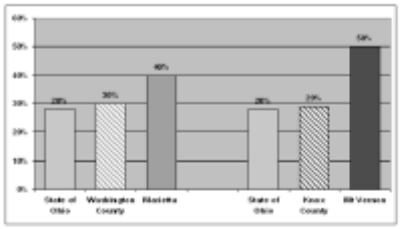
Prevalence of Adult Obesity

- Based on a Body-Mass Index of ≥ 30 kg/m²

No significant difference between the towns



State and county rates obtained from: www.countyhealthrankings.org

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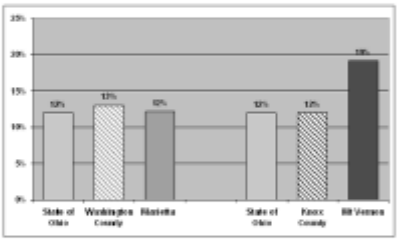
Percent of Uninsured Adults

No significant difference between the towns



State and county rates obtained from: www.countyhealthrankings.org

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Results:
Air Dispersion Modeling and Cumulative Exposure

Ms. Jaime Wagner
US EPA Region 5

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Why was modeling performed?

- U.S. EPA Region 5 was asked to perform air dispersion modeling in support of this health study*
- Results allowed research team to develop a Cumulative Exposure Index (CEI):
  ambient air-Mn ($\mu g/m^3$) × years of residency
- Models can estimate air quality – in this case, manganese concentration in the vicinity of a source
- Model used: EPA's AERMOD modeling system

*U.S. EPA made no conclusions or recommendations — merely provided modeling results.

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What information is required for modeling?

- Meteorological data
  - Winds speed, wind direction, precipitation, etc.
  - Metorol. data obtained from nearby National Weather Service stations.
- Emission information
  - Amount of pollutant emitted
  - Release characteristics (location, height of the stack, how fast the pollutant is coming out of the stack, the temperature of the release, etc.)
- Receptors
  - You have to tell the model where you want it to calculate concentrations; these locations are called "receptors."
- Using this information, the model will predict manganese concentrations in the air at the locations of interest.

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What do we compare the modeling results to?

- Modeled concentrations of air-Mn can be compared to the *Mn reference concentration (RfC).*
- The RfC is the concentration of a pollutant in the air at which we would not expect to see any harmful effects if breathed for a lifetime.
  - Lifetime exposure is assumed to be 24 hours/day for 70 years.
- The ratio of modeled Mn concentration to RfC is known as the *hazard quotient* (HQ). An HQ less than or equal to 1.0 is generally not of concern.
  - If the predicted Mn concentration is less than or equal to the RfC, we expect no harmful effects.
- For manganese, the RfC is 0.05 $\mu g/m^3$ (USEPA, 1993)

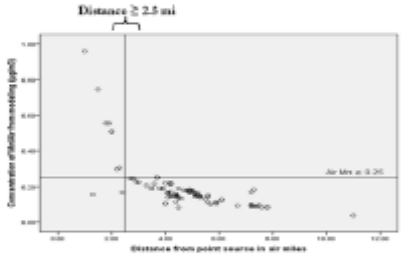
Exposure: Air

	mean	sd	median	min	max
Modeled Mn-air ($\mu g/m^3$)	0.18	0.13	0.16	0.04	0.96
Hazard Quotient	3.69	2.62	3.14	0.77	19.17
CEI* ($\mu g/m^3 \times$ years)	6.67	5.90	5.53	0.89	41.22

N = 100

* CEI = cumulative exposure index

Distance from point source and Air Mn



Higher distance from the source was related to lower concentration of Air Mn (rho = -.758, $p < .000$)

Dispersion Modeling, Hazard Quotient, and CEI: Uncertainties

- Annual Mn emission rate (tons per year) assumed to be emitted equally in grams per second over an entire year
- assume that people breathe the modeled concentration 24 hours a day, 365 days a year over a 70-year lifetime.
- exposure indicators, not a measurements
- do not include human activity patterns or other important variables
- do not take into account changes in emissions over time

Results: Blood Analyses

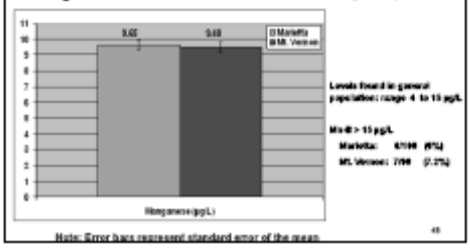
Dr. Harry Roels

Université catholique de Louvain

Manganese in blood

Tests of significance performed on log-transformed values

No significant difference between the towns ($p > 0.05$)



Levels found in general population: range 4 to 15 µg/L

Mn-B > 15 µg/L

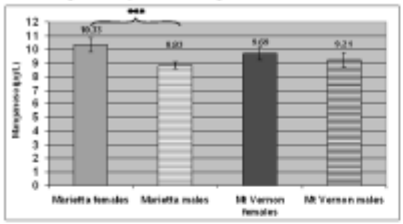
Marietta: 4/100 (4%)

Mt. Vernon: 7/99 (7.1%)

Note: Error bars represent standard error of the mean

Manganese in blood: gender differences

Tests of significance performed on log-transformed values

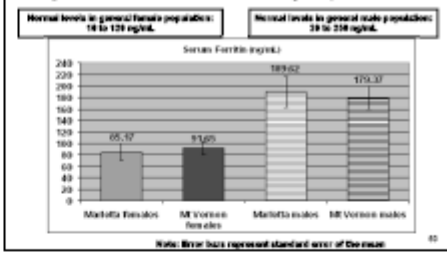


Note: Error bars represent standard error of the mean

Serum Ferritin

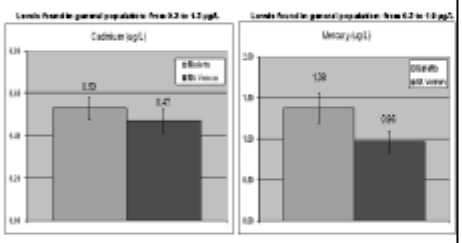
Tests of significance performed on log-transformed values

No significant difference between the towns ($p > 0.05$)



Cadmium and Mercury in blood

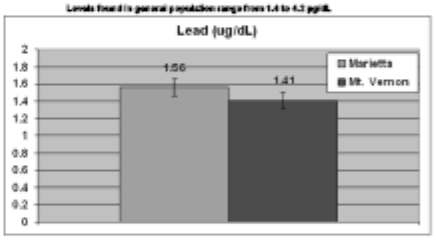
No significant difference between the towns ($p > 0.05$)



Note: Error bars represent standard error of the mean

Lead in blood

No significant difference between the towns ($p > 0.05$)



Note: Error bars represent standard error of the mean

Results:

Relationships between Mn in blood and Mn in air

Mn in blood did not correlate with:

- modeled Mn in air
- CEI
- Hazard Quotient

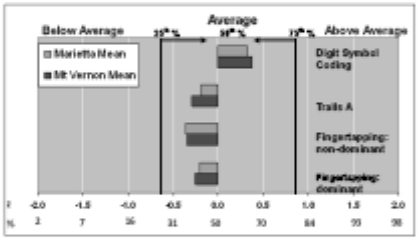
PreliminaryResults: Neuropsychological Testing

Tests of Effort

- All but one participant from Mt. Vernon passed the Rey 15
- This participant was given a more sensitive test of effort, which he/she passed clearly indicating validity of test performance

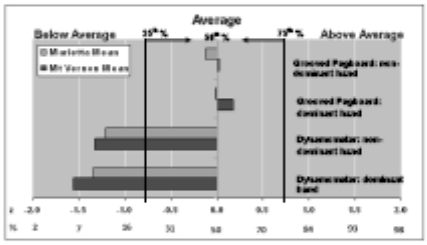
Motor Speed

No significant difference between the towns



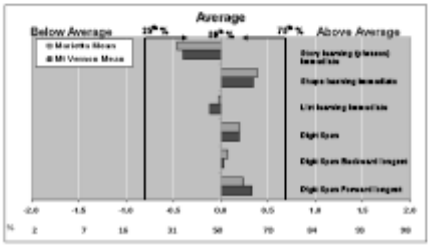
Motor Strength & Tremor

No significant difference between the towns



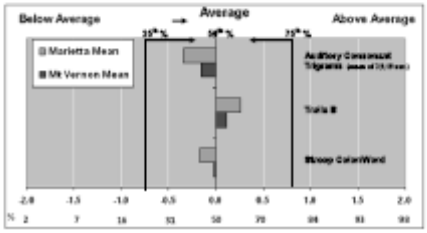
Attention and Immediate Memory

No significant difference between the towns



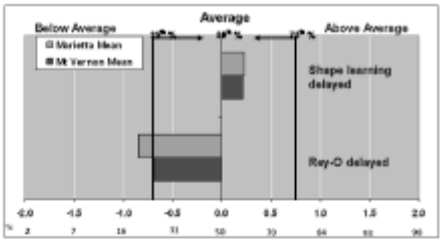
Switching Categories and Divided Attention

No significant difference between the towns



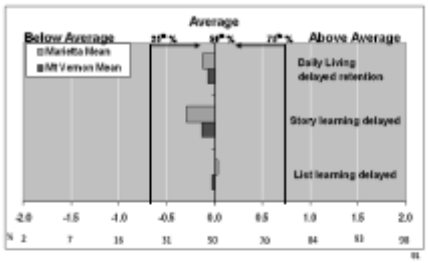
Visual Delayed Memory

No significant difference between the towns



Verbal Delayed Memory

No significant difference between the towns



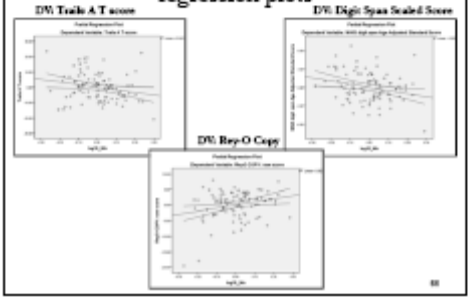
Results:

Relationships between exposure and neuropsychological tests

Mn in blood & test performance

- Analysis: Multiple regressions with log transformed Mn-B as a predictor of test scores, controlling for:
  Examiner * Age * Gender * Education * Mental health medication * Serum ferritin
- No significant relationships in Mt. Vernon
- In **Marietta** (only): Higher Mn-B significantly is associated to
  - Worse scores: Trails A T (b = -16.62, p = 0.05)
  - Better raw scores Rey-O Copy (b = 10.01 , p = 0.02)
  - Worse Scaled Score Digit Span (b = -5.13 , p = 0.02)

Mn in blood & test performance: partial regression plots

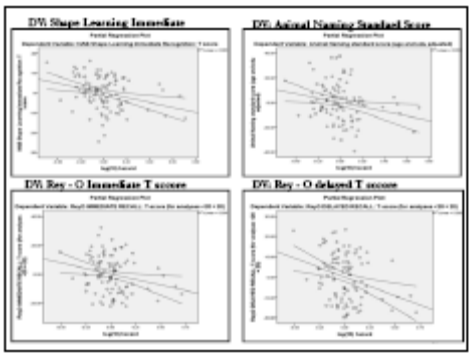


Hazard Quotient & test performance

- Analysis: Hierarchical multiple regressions with the log transformed Hazard Quotient as a predictor of test scores, controlling for:

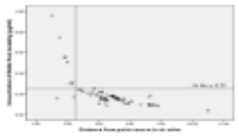
  Examiner * Age * Gender * Education * Mental health medication
- Marietta only
- Higher HQ was related to worse performance on 3 tests of visual memory and 1 test of category naming

  - Specific tests relating to HQ
    - Shape learning immediate (b = -12.28, p < 0.01)
    - Animal Naming (b = -18.28, p = 0.03)
    - Rey-O immediate (b = -16.27, p = 0.03)
    - Rey-O delayed (b = -18.43, p < 0.01)



Modeled Air Mn and neuropsychological performance

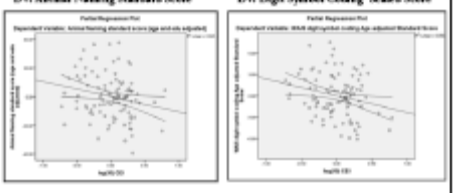
	Closer than 2.5 miles			Farther than 2.5 miles				
	n	Mean	SD	n	Mean	SD	t	p
NAB Shape Learning Immediate Recognition: T score	10	48.80	7.79	90	54.46	8.55	2.00	0.049
Stroop Color T Score	10	38.00	6.02	90	44.39	7.75	2.50	0.014
Rey-Osterreith Immediate Recall: T Score	10	31.30	9.41	90	43.06	13.10	2.90	0.005
Rey-Osterreith Delayed Recall T Score	10	30.60	9.51	90	42.69	12.48	2.96	0.004



CEI & test performance

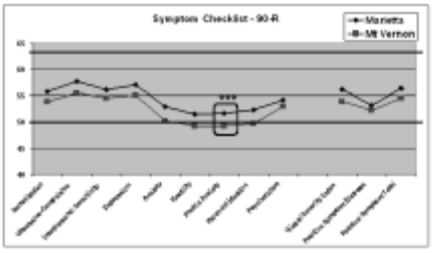
- Analysis: Multiple regressions with the log transformed CEI as a predictor of test scores, controlling for:
  Examiner * Age * Gender * Education * Mental health medication
- Marietta only
- Higher CEI was related to worse performance on
  - Animal Naming (b = -10.60, $p = 0.05$)
  - Digit Symbol Coding Scaled Score (b = -2.35, $p = 0.02$)

CEI & test performance: partial regression plots



Results: Mood

No significant difference between the towns, except for phobic anxiety being higher in Marietta.



Mn in blood & mood

- **Analysis:** Hierarchical multiple regressions with log transformed Mn-B as a predictor of SCL90-R T scores, controlling for:

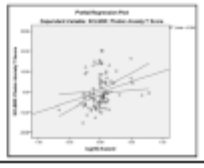
  Gender * Age * Education * Diabetic status * Health insurance status * Mental health medication * Serum ferritin

- No significant relationships in Mt Vernon
- No significant relationships in Marietta

Hazard Quotient & mood

- **Analysis:** Hierarchical multiple regressions with log transformed Hazard Quotient as a predictor of SCL90-R T scores, controlling for:

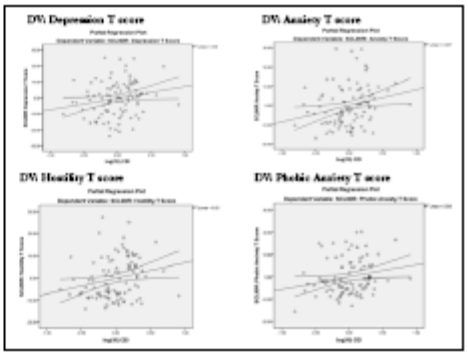
  Gender * Diabetic status * Health insurance status * Mental health medication
- Marietta only
- Higher HQ was related to more phobic anxiety ($b = 10.92$, $p < 0.01$)

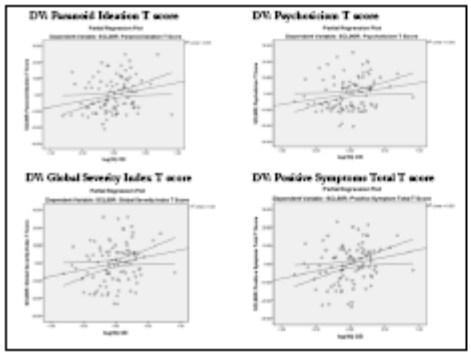


CEI & mood

- **Analysis:** Multiple regressions with log-transformed CEI as a predictor of SCL90-R T scores, controlling for:

  Gender * Age * Education * Diabetic status * Health insurance status * Mental health medication
- Marietta only
- Higher CEI was related to:
  - more depression ($b = 7.57$, $p = 0.04$)
  - more anxiety ($b = 8.43$, $p = 0.02$)
  - more hostility ($b = 8.01$, $p = 0.01$)
  - more phobic anxiety ($b = 6.17$, $p = 0.02$)
  - more paranoid ideation ($b = 8.26$, $p = 0.02$)
  - more psychoticism ($b = 7.19$, $p = 0.04$)
  - more global severity index score ($b = 8.10$, $p = 0.04$)
  - more positive symptoms total ($b = 8.78$, $p = 0.01$)

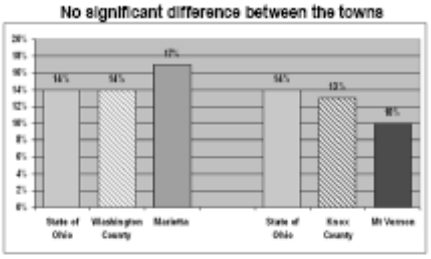




Results:
Health, Illnesses, and Symptoms

Percent of People Reporting Poor or Fair Health

No significant difference between the towns



State and county rates obtained from: www.countyhealthrankings.org

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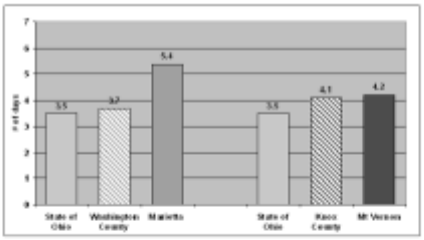
Average Number of Poor Physical Health Days in a Month

No significant difference between the towns

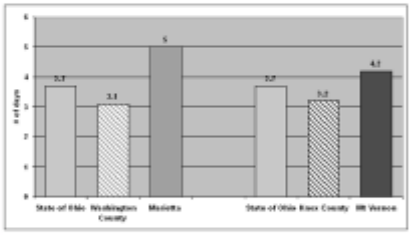


State and county rates obtained from: www.countyhealthrankings.org

80

Average Number of Poor Mental Health Days in a Month

No significant difference between the towns



State and county rates obtained from: www.countyhealthrankings.org

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Individual symptoms significantly different between the towns

Sensory Symptoms & Headaches

	Marietta	Mt. Vernon
Change in sense of smell	14 %	4.4%
Change in sense of taste	10%	0%
Headaches (1x/week or more)	24%	11.1%
Headaches (presence of gait)	13.1%	4.4%
Headaches (presence of pain)	22%	5.6%

Parkinsonism Symptoms

	Marietta	Mt. Vernon
Tightness of facial muscle	8.1%	1.1%

Emotional Symptoms

	Marietta	Mt. Vernon
Feeling anxious	34%	20%
Feeling irritable	39%	17.8%
Change in personality	14%	2.2%

Notes these analyses were performed without multiple comparison adjustment

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Individual symptoms significantly different between the two towns

Other symptoms

	Marietta	Mt. Vernon
Recreation prescription	17%	5.6%
Fever or Chills	8%	0%
Nausea (not fasting related)	12%	3.3%

Notes these analyses were performed without multiple comparison adjustment

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Illnesses

Illness Category	Marietta	Mt. Vernon	Significance
parasitic	1%	0%	ns
neoplasms	10%	10%	ns
emotional	13.2%	10%	ns
eye	16%	25.5%	ns
digestive	6%	4.4%	ns
blood	10.1%	9%	ns
endocrine	21.2%	11.6%	ns
diabetes	13%	10%	ns
nervous system	2%	1.1%	ns
skin	25%	25.8%	ns
genitourinary	19%	27.8%	ns
injury	6%	4.4%	ns
circulatory	37.4%	43.8%	ns
respiratory pneumonia	46.7% 16%	47.8% 27.8%	ns p<0.05
musculoskeletal	48.4%	39.2%	ns

Notes these analyses were performed without multiple comparison adjustment

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Relationship of self-reported diagnosed illnesses and medication use

Medication Category	% who take the medication	% of those who take the medication who were diagnosed with the illness
Circulatory	44.68% →	42.85%
Endocrine	19.58% →	21.62%
Psychiatric	20.21% →	18.42%
Respiratory	12.77% →	70.84%
Musculoskeletal	21.50% →	50%

Relationship between Exposure, Illnesses, and Symptoms

- Manganese in blood
  - After controlling for age, gender, education, and serum ferritin:
  - Mn-B related to higher risk of endocrine ($OR = 15.94$, $p = 0.01$) and psychiatric ($OR = 15.29$, $p = 0.02$) diagnosed illness in Marietta ONLY
  - Related to more frequent reporting of rigidity (stiffness) in the whole group (Marietta + Mt Vernon) ($OR = 6.82$, $p = 0.01$)
- Hazard Quotient
  - After controlling for age, gender, and education:
  - No consistent relationships observed with illnesses
  - Higher HQ was related to more frequent reporting of excessive perspiration ($OR = 1.27$, $p = 0.02$)
- CEI (modeled Mn in air × years of residency)
  - No consistent relationships observed with illnesses or symptoms

Results: Movement and Tremor

- Parallel Lines:
  - No difference between the towns on the Parallel lines test
- CATSYS
  - Participants in Marietta had significantly higher ($p < 0.05$) mean sway, sagittal sway, and sway intensity (Condition 1 – eyes open, no foam)
  - Participants in Marietta had significantly higher ($p < 0.05$) mean sway, sagittal sway, and sway velocity (Condition 3 – eyes open, with foam)
  - No differences on Conditions 2 (eyes closed, no foam) and 4 (eyes closed, with foam)
- UPDRS
  - Participants in Marietta had higher Total Motor ($p = 0.034$) and Bradykinesia ($p = 0.048$) scores than those in Mt Vernon
  - UPDRS correlated with motor test scores (eg. fingertapping, parallel lines)

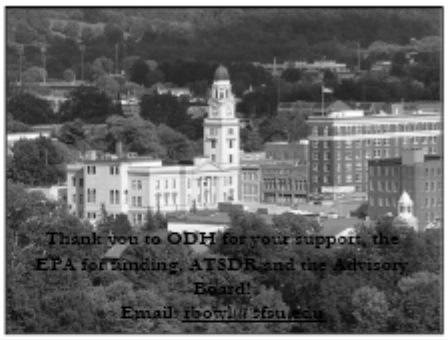
Summary

Summary of Findings

- Significant differences between towns on the following:
  - Participants in Marietta reported significantly more symptoms
  - Marietta participants had slower movement and motor speed than Mt. Vernon participants
  - Participants in Marietta had more body sway under 'eyes open' conditions, but no differences under the 'eyes closed' conditions
- Mn in blood
  - Related to more frequent occurrence of diabetes and psychiatric illness in Marietta
  - Related to more frequent reporting of rigidity (stiffness) in both towns
- HQ
  - Higher HQ was related to:
    - Worse performance on three tests of visual memory and one of category fluency
    - Higher phobic anxiety
    - More frequent reporting of excessive perspiration
    - No consistent relationships observed with illnesses
- CEI
  - Higher CEI was related to:
    - Worse performance on two tests of processing speed
    - Worse mood
    - No consistent relationships observed with illnesses or symptoms

Conclusions

- Overall, results of this epidemiologic study using random sampling did not support clear-cut findings of adverse health effects from Mn in air and blood in the town of Marietta
- This is supported by the lack of differences between Marietta and Mt Vernon on neuropsychological tests
- Increased air exposure to Mn (proximity to the point source) is related to visual memory and two tests of processing speed
- Overall neuropsychological test results are within the average range of the general population



For additional questions:

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Website – active after June 24th:
http://online.sfsu.edu/~mnstudy/

Any questions?

Appendix E

Manganese Exposure in Adults: An Epidemiologic Study of Symptoms, Mood Effects, Motor and Neurological Function

Rosemarie M. Bowler, Ph.D., M.P.H.

Abstract

Background: Manganese (Mn) is a neurotoxin associated with mood, medical symptoms, motor and neurological effects. Reports of adverse health effects from occupational exposure to Mn are common but environmental reports of airborne Mn effects are sparse.

Methods: A random sample of 100 adult Mn exposed residents was studied with a neurological examination, motor function and mood tests, and a comprehensive health questionnaire. Results are compared with 90 randomly selected residents from a demographically similar control town. Mn in blood and air were measured.

Results: Exposed residents reported significantly more sensory, Parkinsonism, and emotional symptoms, and had higher SCL-90-R Phobic Anxiety scores. The Cumulative Exposure Index, based on modeled Mn/air and length of residence, was related to 6 of 9 SCL-90-R clinical scales and 2 of 3 global scales. No differences in Mn in blood between the towns were observed. Anxiety and Phobic Anxiety scores were significant predictors of symptoms, diagnosis of Anxiety Disorder and use of anti-anxiety medications in the whole sample and motor and neurological dysfunction (UPDRS bradykinesia and ADL) in exposed residents only.

Conclusion: Symptoms and measured anxiety and phobic anxiety seem to be the cardinal signs and results in this study. Strong relationships between exposure, symptoms, and mood disturbance add validity to an association with Mn exposure and highlight the importance of measuring Anxiety, Phobic Anxiety and symptoms in relationship to function. The methods of this first epidemiologic study of Mn exposure of adults in the U.S. should be applied to communities with higher levels of Mn exposure.

Submitted to the International Neuropsychological Society Meeting, Boston, MA 2011

Appendix F

Manganese Exposure and Components of Executive Function in Environmentally-Exposed Adults

Harris, M[1].; Bowler, R[2].
[1]Alliant International University [2]San Francisco State University

Background: Manganese (Mn) is a neurotoxin, which in addition to well-documented motor effects, is related to a wide variety of cognitive effects. The effects of Mn exposure on components of executive functioning are not well-studied, particularly with environmental Mn exposure.
Methods: One-hundred adult participants were randomly selected from Marietta, OH, which houses the largest Mn-producing plant in the US. Participants completed a battery of neuropsychological tests. Confirmatory factor analysis of tests supported three factors representing components of executive functioning: A*ttention/Mental Tracking (ACT, NAB List Learning – Semantic Clustering, and WAIS-III Digits Backwards), Cognitive Flexibility (Trails B-A, Stroop Interference, and Animal Naming), and Planning/Organizing (ROCFT Immediate and Delayed Recall)*. Air-modeling analyses calculated an estimated level of airborne Mn exposure (Mn/Air) for each participant.
Results: Structural Equation Modeling (SEM) showed strong overall fit (X^2_{35} = 45.071, p = .118; CFI = .968; RMSEA = .044) for a model with Mn/Air significantly predicting Planning/Organizing (p = .01) and Cognitive Flexibility to a lesser degree (p = .05), but not Attention/Mental Tracking (p =. 81), with age and education levels accounted for. Error terms for Mental Tracking/Attention and Cognitive Flexibility showed significant covariance with each other (p = .01).
Conclusion: Results indicate that despite low levels of exposure, higher Mn exposure affects planning/organizing and cognitive flexibility, but not mental tracking/attention. This suggests a hierarchy of effect, where Mn has a greater effect on the complex planning/organizing component of executive function, but a smaller effect on attentional/mental tracking processes.

Appendix G

Relationship of airborne manganese exposure to biomarkers of blood and serum controlled for Ferritin with neurological and neuropsychological test results in adults*

Rosemarie M. Bowler, San Francisco State University

An extensive neuropsychological battery was applied in 2 communities to evaluate the effect of Mn exposure from the only operating Mn alloy production plant in the U.S. Study participants (n = 191), 30-75 years of age, were recruited at random, with approximately equal proportions of women and men in the exposed and control towns. Blood analyses were carried out by the CDC Laboratory for Mn, Cd, Pb and Hg. Serum was analyzed for ferritin, a potential confounder competing for the transport of Mn in the brain. Modeled air concentrations were computed in a hazard index (HI) and a cumulative exposure index (CEI) using air Mn, duration of exposure and distance from the source. The test results were compared to Mn in blood and serum, controlled for ferritin. In hierarchical regressions, the log transformed CEI was a significant predictor for category fluency, digit symbol and the HI was related to visuospatial learning, category fluency and executive function. CEI and HI significantly predicted Generalized Anxiety.

Submitted to the International Neurotoxicology Association (INA) Meeting in Xian,China – June 2011. Funding by the U.S. EPA, under Co-operative Agreement No 83416001.

Appendix H

Harris, M. (2011) Manganese Neurotoxicity: Relationships Between Exposure, Executive Function, and Mood Among Environmentally-Exposed Adults. *Dissertation Abstracts International*

Manganese (Mn) is a neurotoxin, which in addition to well-documented motor effects, is related to a wide variety of cognitive and mood effects. The relationship between Mn exposure, mood, and components of executive function has not been explicated in depth in previous studies, particularly with environmental Mn exposure.

One-hundred adult participants were randomly selected from Marietta, OH, which houses the largest Mn-producing plant in the US. Participants completed a battery of tests on neuropsychological and mood functioning. A cumulative exposure index (CEI) was created using air-modeling analyses to calculate an estimated level of airborne Mn exposure for each participant.

Structural Equation Modeling (SEM) showed strong overall fit for a model with mood (as measured by SCL-90R Anxiety and Depression subscales) mediating the effect of CEI on components of executive functioning (Working Memory, as measured by WAIS-III Digits Backward and Auditory Consonant Trigrams, and Cognitive Flexibility / Response Inhibition, as measured by Trails B / A, Stroop interference scores, and Animal Naming), accounting for education. Residuals for Working Memory and Cognitive Flexibility / Response Inhibition showed significant covariance with one other.

This is the first study to focus on the relationship between Mn, mood, and executive functions in cases of environmental exposure to Mn. Results indicate that despite low levels of exposure, greater Mn exposure effects mood functioning, which in turn affects the Working Memory and Cognitive Flexibility / Response Inhibition components of executive functioning.

Appendix I

Int J Hyg Environ Health. 2011 Nov 21. [Epub ahead of print]

Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohiocommunity with environmental airborne manganese exposure.

Bowler RM, Harris M, Gocheva V, Wilson K, Kim Y, Davis SI, Bollweg G, Lobdell DT, Ngo L, Roels HA.

Abstract

Manganese (Mn) is a nutrient and neurotoxicant sometimes associated with mood, motor and neurological effects. Reports of health effects from occupational exposure to Mn are well known, but the reported links to environmental airborne Mn (Mn-Air) are less conclusive. Marietta, OH (USA) is a previously identified community with elevated Mn-Air from industrial emissions. Households were randomly selected in Marietta and the comparison town (Mount Vernon, OH). The responders were used to recruit on a voluntary basis 30- to 75-year-old residents, i.e. 100 in Marietta and 90 in Mount Vernon. They were administered the Unified Parkinson's Disease Rating Scale (UPDRS), motor efficiency, and mood tests, along with a comprehensive questionnaire including demographics, health and work history. Blood Mn (MnB), serum ferritin, and hepatic enzymes were measured. Results were compared with those of 90 residents from a demographically similar comparison town, Mount Vernon, OH, where Mn-Air from industrial emissions was not of concern. Mn-Air exposure indices were modeled for Marietta residents. The Mn-exposed participants resided on average 4.75 miles (range 1-11) from the Mn point source. Their modeled residential Mn-Air estimate ranged from 0.04 to 0.96μg/m(3) and was on average 0.18μg/m(3). The group means of MnB were similar for the Mn-exposed (9.65μg/L) and comparison (9.48μg/L) participants. The Marietta group reported more generalized anxiety on the Symptom Checklist-90-Revised (SCL-90-R) than the comparison group (p=0.035). Generalized anxiety in Marietta was related to a cumulative exposure index (p=0.002), based on modeled Mn-Air concentration and length of residence. Higher generalized anxiety scores were related to poorer performance on UPDRS tests [adjusted relative risk (95%CI): 2.18 (1.46-3.25) for motor-related activities of daily living, 3.44 (1.48-7.98) for bradykinesia, and 1.63 (1.06-2.53) for motor/movement]. Group differences in SCL-90-R generalized anxiety between the two towns and the observed relationship between exposure indices and generalized anxietysuggest an association between environmental Mn exposure and anxiety states. Whether this association is due to direct neurotoxic effects of Mn-Air or concern about the health effects of air pollution remains an open question. The results highlight the importance of measuring anxiety in relation to neuropsychological and neurological endpoints, and should be validated in other studies of Mn-exposed communities.

Appendix J

Neurotoxicology. 2011 Oct;32(5):606-14. Epub 2011 Aug 4.

Motor function in adults of an Ohio community with environmental manganese exposure

Kim Y, Bowler RM, Abdelouahab N, Harris M, Gocheva V, Roels HA.

OBJECTIVES:
The objective of the present study was to evaluate motor function in order to assess the effects of long-term, low-level environmental manganese (Mn) exposure in residents of an Ohio community where a large ferro- and silico-Mn smelter has been active for more than 50 years.

METHODS:
One hundred residents from the Mn-exposed Ohio community were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), a postural sway test, and a comprehensive questionnaire exploring demographics and general health. The results were compared to those of 90 residents from a demographically similar comparison town in Ohio. Mn exposure was assessed using modeled airborne Mn and blood Mn (Mn-B). The UPDRS was employed to evaluate parkinsonian motor features. Postural sway was measured using a CATSYS 2000 (Danish Product Development).

RESULTS:
No significant difference between the exposed and comparison groups was evident as to Mn-B, demographics or major health outcomes. The risk of abnormal UPDRS performance using "Motor and Bradykinesia" criteria was increased in the Mn-exposed group after adjustment for potential confounders such as the presence of other neurotoxic metals, factors affecting susceptibility to Mn, potential factors influencing motor performance, and other possible demographic confounders. No participant was diagnosed with clinical manganism by neurological examination. After adjustment for various potential confounders, the Mn-exposed group showed significantly higher postural sway scores under eyes-open conditions than the comparison group.

CONCLUSIONS:
Subclinical findings on the UPDRS and postural sway in the Mn-exposed group may possibly reflect early subtle effects of chronic low-level Mn exposure. However, the cross-sectional study design, the small to medium effect sizes, and the little biological plausibility are limiting the possibility of a causal relationship between the environmental Mn-air exposure and the early subclinical neurotoxic effects observed.